CONFIDENTIAL

Evidence review: denosumab for the prevention of osteoporotic fractures in post-menopausal women.

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Contributions of authors

Pamela Royle, Rob Henderson, Rosemary Hollick and Norman Waugh reviewed the evidence on clinical effectiveness. Rosemary Hollick provided clinical advice.

Graham Scotland reviewed the cost-effectiveness section, re-ran some modelling, and carried out sensitivity analyses. Paul McNamee and Norman Waugh provided comments on the economics critique.

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Abbreviations

BMD	bone mineral density
BMI	body mass index
BNF	British National Forumlary
BP	bisphosphonate
CI	confidence interval
DIVA	Dosing IntraVenous Administration
EQ-5D	EuroQol-5D
FDA	U.S. Food and Drug Administration
FREEDOM	Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months
GMS	General Medical Services
GP	general practitioner
GPRD	General Practice Research Database
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
HR	hazard ratio
HRQOL	Health-related quality of life
HRT	hormone replacement therapy
HTA	Health technology assessment
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IV	intravenous
LY	Life years
MPR	medication possession ratio
MTC	mixed treatment comparison
NCCNSC	National Collaborating Centre for Nursing & Supportive Care
OBPs	oral bisphosphonates
QALY	quality adjusted life year
PMO	postmenopausal osteoporosis
PSA	probabilistic sensitivity analysis
RA	rheumatoid arthritis
RR	relative risk
sc	subcutaneous
SD	standard deviation
TA	technology appraisal
WHO	World Health Organization
WTP	willingness to pay

1. SUMMARY

1.1 Scope of the submission

The submission from Amgen was much longer than recommended in the NICE guidance to manufacturers. The initial submission was 486pages long (though that includes about 60-70 pages of text from NICE) with about 600 pages of appendices.

NICE has provided the following statement:

The manufacturer originally provided a submission of 468 pages. NICE requested that a more concise submission be provided because the exceptionally extensive length of the original submission would lead to difficulties in the course of the appraisal. The manufacturer provided a shorter restructured submission, with some information moved to the appendices.The manufacturer pointed out that there were a number of factors which in their view necessitated the length of the original comprehensive submission, most notably being the volume of comparators included in the final scope, the complexity of existing NICE guidance in osteoporosis (TA160/161) and the unusually high volume of denosumab data available at the time of launch."

The main part of the submission was reduced to 314 pages, partly by transferring material into the appendices, which grew to 827 pages. The revised submission was received on 15th February.

The initial submission contained a large amount of material on trials which had bone mineral density as the outcome. Given that there are trials of denosumab and the key comparators which report fracture rates, data on BMD were not required. In the revised submission, some of the details of these trials was moved to appendices, but a lot was retained in the main submission, and was not relevant.

Amgen stated that (pages 14-15);

"*Given the wide availability of generic BPs in the UK, denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable".*

Despite this, the initial Amgen submission included many comparisons of denosumab against the oral BPs. These were irrelevant if denosumab is to be used in women for whom oral BPs are not tolerated or contra-indicated.

The submission also included much detail on morphometric or radiological fractures, which include vertebral fractures detected only on X-ray, which had not caused women to seek medical help, and where the term "fracture" includes diminution in size of vertebral bodies. The fractures which matter are "clinical fractures". Radiographic-only fractures were, correctly, not included by Amgen in the modelling, and so the details could have been omitted from the submission.

Because of the size of the submission and the tight timescale, the ERG does not guarantee that all details have been captured.

Some sensitivity analyses in the submission used the FRAX algorithm. The ERG did not receive permission to use this until 19th March, too late to run any checks.

1.2 Summary of submitted clinical effectiveness evidence

The main pieces of evidence submitted were details of the FREEDOM trial of denosumab against placebo, and an indirect comparison of denosumab against other drugs for osteoporosis.

The FREEDOM trial was a large good quality trial in 7,868 women with post-menopausal osteoporosis. It showed that denosumab given by subcutaneous injection at 6-monthly intervals for 3 years was effective in reducing fractures. Hip fractures were reduced by 40%, from 1.2% of women in the placebo group to 0.7% in the denosumab group. Clinical vertebral fractures were reduced by 69% from 2.6% in the placebo group to 0.8% in the denosumab group.

Safety data are available from 30 studies, giving a total of 14,000 patients, of whom 11,000 are in post-menopausal women. Denosumab appears safe.

Persistence with osteoporosis treatment is known to be poor for many existing drugs such as the oral bisphosphonates. The industry submission presents data from the General Practice Research Database showing that [redacted]. Adherence to denosumab in routine care will not be known for some years, but is it likely that the 6-monthly administration in GP surgery or hospital clinic will encourage persistence.

The control group in the FREEDOM trial were given placebo. This has been criticised on ethical grounds but was mandated by the regulatory authorities. The effectiveness of denosumab relative to other bone loss therapies was therefore estimated from an indirect comparison using trials of other drugs against placebo. This is not ideal but is the best that could be done in the absence of head to head to head trials.

The Amgen submission stated that because of the availability of inexpensive generic oral bisphosphonate (weekly alendronate costs about £15 a year), "denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance.". The drugs used in the indirect comparison were therefore strontium, raloxifene, teriparatide, zoledronate and intravenous ibandronate (with results from a trial of oral ibandronate being assumed to reflect those of IV ibandronate – data from a trial which showed IV ibandronate to be more effective than oral were not used). Teriparatide is very expensive and its use is restricted by NICE guidance, and it would not be a comparator in most women.

The indirect comparison produced relative risks of fracture for denosumab compared to other drugs. [redacted]

Zoledronate is given by IV infusion once a year. In women unable to take oral BPs, the ERG considered that zoledronate is a highly relevant comparator to denosumab.

1.3 Summary of submitted cost effectiveness evidence

Amgen provided multiple comparisons of cost-effectiveness using a high quality model which took account of costs from short-term drug costs to long-term nursing home costs (the latter because after hip fracture, many elderly women lose independence).

The analysis complied with the NICE reference case.

The submission reported that denosumab;

- dominated strontium, i.e. was both more effective and less costly

- was cost-effective compared to raloxifene with costs per QALY of £9,289 in women without a previous fracture and around £2,000 in those with a previous fracture.

- could be cost-effective compared with no treatment in some subgroups of women without prior fracture, who might not be treated with a second drug if unable to tolerate alendronate, according to the current NICE guidance. The ICER versus no treatment falls below £30,000 per QALY in women over 75 with a T-score of -2.5 or below, women over 65 with a T score <= -3, and women over 55 with a T-score <= -4. Note that this assumes Amgen's costs of administration are correct.

- could be cost-effective versus no treatment in women with fragility fractures (£12,381 per QALY).

- dominated IV ibandronate

- was cost-effective compared to zoledronate with ICERs for zoledronate versus denosumab reported to be £70,000 per QALY in women with no prior fracture and £29,000 in women with a prior fracture.

However, a key assumption was that denosumab would be given in general practice at the average cost of two standard GP visits. This would make it much less costly than zoledronate, which was assumed to be given in hospital clinics. Given the similar effectiveness of denosumab and zoledronate, the cost-effectiveness comparison depended largely on the relative costs.

1.4 Commentary on the robustness of submitted evidence

Strengths

The key trials were of good quality, had large numbers of recruits and adequate duration. The Horizon trial of zoledronate, the main comparator, recruited 7,765 women. The economic model was of high quality. The submission and appendices provided very detailed accounts of underlying assumptions and sensitivity analyses.

Weaknesses

The first problem with the submitted evidence was the volume, due to the presence of much irrelevant material. We did not consider the evidence of effects of drugs on bone mineral density to be relevant, partly because of doubts about the value of BMD in assessing effects

of most drugs in osteoporosis, but mainly because there were fracture data for all the drugs. Nor did we consider the data on morphometric vertebral fractures to be useful, and it should be noted that Amgen did not use such data in the modelling.

The submission argued that zoledronate and IV ibandronate should not be primary comparators because they were "not standard care" and because they had not been appraised by NICE. However despite not having been appraised by NICE, both have been licensed for some time and are in routine use in the UK.

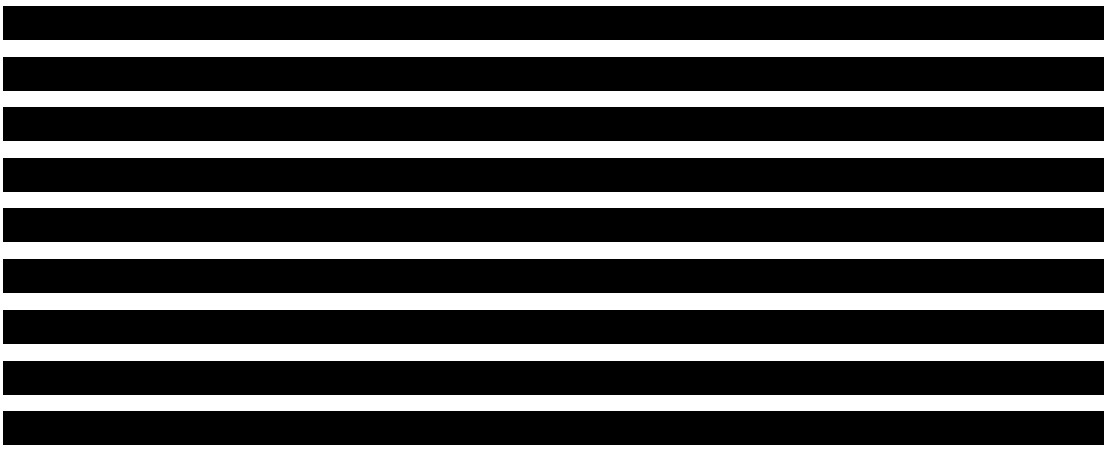
The major weakness lay in the economic modelling of zoledronate versus denosumab. The ERG considered that zoledronate is the key comparator. The relative cost-effectiveness depended on the assumptions about relative costs, which were that;

- Denosumab would be given twice a year in general practice at the cost of two GP visits

- Zoledronate would be given once a year in hospital clinics

The ERG considers it unlikely that denosumab would be started in general practice. While it currently appears safe, it is a new biological agent with effects on other body systems than bone, including the immune system, and long-term adverse events cannot be entirely ruled out.

The ERG had doubts as to whether, if primary care staff did administer denosumab, GPs would provide it as part of general medical services. It is more likely that it would be regarded as an enhanced service for which payment would be negotiated. The size of such payment is not yet known. Thus the ERG felt there was potential for the average cost of 2 GP visits to underestimate the marginal per patient costs to trusts of providing denosumab in primary.care. The manufacturer disputed this point as summarised in section 5.2.6.



Areas of uncertainty

The indirect comparison was necessary because of the lack of direct head to head trials. It appeared well done, but the ERG wondered if differences in baseline characteristics of the women in the trials (such as duration of follow-up, age, BMI, proportion with previous fractures) would affect some comparisons.

Because of absence of data on the effect of zoledronate on wrist fractures, the modelling assumed that it would not reduce the incidence of those, whereas it was assumed that denosumab would, based on data from the FREEDOM trial (though the 95% CI was 0.64 to 1.11). However given the equivalence, or a non-significant slight superiority of zoledronate to denosumab, the ERG considered it unlikely that zoledronate would have no effect on wrist fractures.

In the modelling, the reduction in breast cancer incidence from raloxifene treatment was not included. This was queried with Amgen, whose response was that this was in line with the precedent set in Technology Appraisals 160 and 161.

In the indirect comparison, data from a trial of oral ibandronate were used, and assumed to apply to IV ibandronate. However, the DIVA trial of oral versus IV ibandronate showed that the IV form, given at three monthly intervals, was more effective with fracture incidence of 4.8% in the IV groups versus 6.2% in the oral group. This difference was at 2 years follow-up and was not statistically significant, but it could be used in a sensitivity analysis.

1.5 Key issues

The effectiveness of denosumab is not in doubt, and it appears safe. The key issue in cost-effectiveness analysis is its cost relative to zoledronate. For women with no prior fragility fractures, its potential cost-effectiveness relative to no treatment in some groups is also highly relevant, since current NICE guidance recommends no treatment for many women in this group if they cannot tolerate alendronate.

2. BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

Amgen gave a brief but accurate description of the health problem, focusing on osteoporosis in post-menopausal women as requested in the NICE scope.

2.2 Critique of manufacturer's overview of current service provision

There are few problems with the description of current service provision. It gives details (from GPRD) of current prescribing in primary care. This means that data on drugs administered in hospital are not captured. This section also summarises current NICE guidance (TA 160 and 161)[1,2] and the scope for the guideline, development of which is currently suspended.

There are some issues with Amgen's view of future service provision of denosumab. It is administered twice a year by subcutaneous injection. They expect it to be given in general practice at the average cost of two GP visits per year, and contrast this with the costs of zoledronate, given by IV infusion in a hospital setting. Some monitoring of zoledronate treatment may be incorporated into the infusion visit

It seems unlikely that general practitioners would start patients on such a new biological agent without specialist advice, and so we would expect at least one OP visit to be required. In many cases, we would expect continued hospital follow-up. If follow-up was partly or mainly in general practice, we doubt if it would be regarded as part of GMS, and would expect it to be covered by an enhanced service agreement at a negotiated cost (which may or may not work out to be greater than the average cost of two GP visits per patient). Advice from one English PCT was that the local formulary committee would class a new biologic agent as for hospital prescription only. It should be noted that in addition to its effects of bone, denosumab might affect the immune system, because it acts by inhibiting RANKL which is involved in lymphocyte differentiation .[3] There would be a case for creating a registry of all users, similar to that proposed for the new biological anti-TNFs used in RA. A call-recall system would also have to be put in place.

The subcutaneous injection of the drug could be given by a GP, or a practice nurse, or indeed by the patient herself, as happens with other drugs administered subcutaneously, such as beta-

interferon for multiple sclerosis and teriparatide for osteoporosis

[redacted]

With only twice yearly dosing, it may not be regarded as worthwhile training women to give it themselves since they will presumably visit the practice to obtain the pre-filled pen injection device. After six months, some might have forgotten how to give it, unlike with drugs given daily like teriparatide.

In summary, while the injection will be simple, and could be given by practice nurse or possibly the patient herself, our expectation is that denosumab might not be seen as part of General Medical Services (GMS), and that practices would regard it as part of an enhanced service. We are uncertain if the average costs assigned to GP visits in the manufacturers model accurately reflect the per patient costs that trusts would face if implementing such a service.

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population and technology

The population of interest is correctly identified in the submission, as being post-menopausal women with osteoporosis as defined by the WHO: *A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Osteoporosis is further defined as a bone mineral density at spine or hip with a T-score below -2.5 standard deviations (SDs) of the normal level in a 20-year old woman.*

As the submission says (page 31), osteoporosis is a major problem, in that:

- It is estimated that there are 180,000 osteoporosis related fractures each year in England and Wales, mostly in women

- Of these, 70,000 are hip fractures, which require hospital admission and surgical treatment, and which are associated with a significant mortality, both in the short term and the long term. Some of the mortality will be unrelated to osteoporosis, but a recent meta-analysis by Bolland and colleagues noted that treatment of osteoporosis did reduce mortality (relative risk 0.9, 95% CI 0.81-1.0; p= 0.044).[5] This reduction was derived from pooling results for all drugs. Only one individual trial of zoledronic acid showed a statistically significant reduction (RR 0.72, 95% CI 0.56 – 0.91).[6] Most trials were not powered to show mortality reductions.

- There are about 25,000 clinical vertebral fractures and 41,000 wrist fractures (data from NICE 2008). The term "clinical vertebral fracture" is used because most vertebral "fractures" do not cause sufficient symptoms to result in presentation for medical help. It may be useful to think of most vertebral fractures being not a broken bone but a compressed one.

- In women over 50 years, the lifetime risk of a hip fracture is one in five

The technology is denosumab, the first drug of its class. Normal bone is in a continuous state of breakdown and renewal. Breakdown is carried out by cells called osteoclasts and renewal

by osteoblasts. Denosumab is a monoclonal antibody which reduces osteoclast activity and hence bone breakdown.

3.2 Comparators

NICE issued guidances on drugs for osteoporosis in October 2008, Technology Appraisals (TA) 160 and 161. [1,2] TA 160 dealt with primary fracture prevention, and recommended that the oral bisphosphonates (OBPs) alendronate, risedronate and etidronate be used in osteoporosis, with alendronate first choice, and with some restrictions on the others based on cost-effectiveness. TA 160 also recommended that strontium ranelate be used in women unable to use OBPs. It said that raloxifene should not be used for primary prevention of osteoporotic fractures.

TA 161 dealt with secondary prevention – i.e. prevention of factures in women who had already had one or more clinically apparent previous fractures. A history of a fracture is a strong predictor of future ones. Alendronate was again the drug of first choice, with the other OBPs being recommended in women unable to use alendronate, but with some restrictions based on cost-effectiveness. Strontium ranelate and raloxifene were also recommended but restricted to women unable to take OBPs, and to certain thresholds based on age and risk factors.

One controversial issue has been that the effect of the restrictions means that if women are recommended to be treated with alendronate but cannot take it, they may not qualify for the other drugs. This is because alendronate is generic and cheap, and the others much more expensive. So their physicians are faced with a situation in which they have told the patient that treatment is required, but then if a woman cannot take alendronate, she should not be treated with another drug till her condition worsens.

Table 1 shows the annual costs of the drugs. Note that these costs do not include administration costs.

Table 1 Costs of osteoporosis drugs

Drug	Brand	Dose	Route of administration -Frequency	Cost as per BNF 59 March 2010	Cost per year
Alendronate	Generic	10mg	Oral - Daily	28 tab pack =£2.30	£29.98
		70mg	Oral - Weekly	4 tab pack =£1.16	£15.08
Denosumab	Prolia	60mg	SC – twice yearly		£366
Etidronate	Didronel	400mg	14/90 day cycle	1 pack =£20.29	£82.29
Ibandronate	Bonviva (tablet)	150 mg	Oral - Monthly	3 tab pack = £55.21	£220.84
	Bonviva (injection)	3 mg	IV - 3 Monthly	3 mL prefilled syringe =£68.64	£274.56
Raloxifene	Evista	60 mg	Oral - Daily	28 tab pack=£17.06	£222.39
Risedronate	Actonel (daily)	5 mg	Oral - Daily	28 tab pack =£18.36	£239.34
	Actonel (weekly)	35 mg	Oral – Weekly	4 tab pack = £19.51	£253.63
Strontium	Protelos	2 gm	Oral - Daily	28 sachets = £25.60	£333.71
Teriparatide	Forsteo	20 micrograms daily	SC - Daily	3 mL prefilled pen for 28 doses = £271.88	£3544.15
Zoledronate	Aclasta	5mg	IV - Yearly	100 mL bottle = £283.74	£283.74

The main problem with the Amgen submission was the choice of comparators. Having stated that the place of denosumab would be in women who could not tolerate oral BPs, or in whom oral BPs were contra-indicated, the submission identifies strontium and raloxifene as the primary comparators. This is in line with current NICE guidances. In theory, teriparatide should also be included, but use of that is very restricted by the NICE guidance, and Amgen argue, reasonably, that is should not be regarded as a comparator, and it is included as a "secondary comparator".

The current NICE guidance does not include zoledronate and ibandronate. However these are both in common use. Zoledronate is given as a once a year injection. Ibandronate can be

given orally once a month or IV every three months. Amgen have (page 15) rather dismissed these as "not standard care", and regarded them as secondary comparators. However, zoledronate should also be regarded as a primary comparator, in patients who cannot take oral BPs, on grounds that it is licensed in the UK and has similar convenience and efficacy. Table 2 gives efficacy data for denosumab and zoledronate from the key trials, both against placebo. The results show that zoledronate is as good as denosumab. Zoledronate was approved by the Scottish Medicines Consortium (February 2008) for use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis.[7] The EU patent will expire in 2012 (Datamonitor report July 2009).[8]

Ibandronate has also been approved by SMC in both oral (SMC January 2006) and IV (August 2006) forms.[9,10]

Table 2 Results for denosumab and zoledronate.

	Clinical vertebral fracture	**Hip fracture**	**Non vertebral fracture**
FREEDOM Trial[11]			
Denosumab no. (%)	29 (0.8)	26 (0.7)	238 (6.5)
Placebo no. (%)	92 (2.6)	43 (1.2)	293 (8.0)
Relative Risk or Hazard Ratio (95% CI)	0.31 (0.20 to 0.47)	0.60 (0.37 to 0.97)	0.80 (0.67 to 0.95)
P value	<0.001	0.04	0.01
HORIZON Trial[12]			
Zoledronic Acid no. (%)	19 (0.5)	52 (1.4)	292 (8.0)
Placebo no. (%)	84 (2.6)	88 (2.5)	388 (10.7)
Relative Risk or Hazard Ratio (95% CI)	0.23 (0.14 to 0.37)	0.59 (0.42 to 0.83)	0.75 (0.64 to 0.87)
P value	<0.001	0.002	<0.001

In the indirect comparison, Amgen include oral ibandronate but not IV ibandronate, on the grounds that (page 105) "no data for iv ibandronate were identified". The DIVA (Dosing Intra Venous Administration) trial compared injected ibandronate, given at 2-monthly or 30

monthly intervals, with daily oral ibandronate. The primary outcome was BMD. However, the 2-year results from Eisman and colleagues (2008) also provide fracture data.[13] The incidence of clinical osteoporotic fractures was lower in the IV groups than in the oral group – 4.8% versus 6.2%, a difference which was not statistically significantly better. However the key point is that IV ibandronate is at least as good as oral ibandronate, and should be regarded as a valid comparator. The BMD results were highly significantly better, and it is likely that longer follow-up and larger numbers would confirm significant superiority in fractures too. However the correlation between BMD and fracture risk is far from perfect (see below).

3.3 Outcomes

The key outcomes are fractures, with the main groups being;

- Hip fractures
- Clinical vertebral fractures
- Wrist fractures ("Colles fractures")
- Other fractures

Other outcomes include safety and adherence.

3.3.1 Adherence to osteoporosis therapy

Adherence is a very important issue, since various studies report poor adherence, and others show that poor adherence increases fracture risk. It is given appropriate attention in the Amgen submission, with data from the GPRD (section 5.8).

Adherence, Persistence & Compliance - definitions

In the Amgen submission, adherence is defined as a '*general term encompassing … persistence and compliance*'

Persistence is defined as '*… the duration of time from initiation to discontinuation of therapy*'. Essentially, persistence is about <u>how long</u> patients take a recommended course of treatment.

Compliance is defined as '*… the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking. … Compliance can be measured by the number of doses taken divided by the number of prescribed doses during a defined time period period, also known as MPR.*'

Elsewhere in the submission, MPR (medication possession ratio) is defined as '… *the sum of the days supply of medication divided by the number of days between the first prescription and the end of the duration of the last prescription*.'

Essentially, compliance quantifies the extent (how much) to which patients took a recommended course of treatment as advised.

Therefore, it is possible that a patient may be highly persistent (i.e. take a recommended course over a prolonged period of time) but show poor compliance (i.e. take on alternate days a medication that should be taken daily.) Equally, a patient may not persist on a medication but be highly compliant while taking it.

Adherence, Persistence & Compliance – Literature Review

In the submission, several papers are cited relating to adherence with oral bisphosphonate (BP) therapy. (section 2.5)

The submission states that evidence exists which shows that '… *persistence and compliance with oral BPs is poor, primarily as a result of the strict and complex dosing regimen*.'

In relation to oral BPs, the submission also states that '… *the percentage of patients discontinuing treatment within 1 year has been reported as at least 42% and the median duration of BP treatment has been estimated to be as low as 1.2 years.*' (page 38)

Furthermore, the submission states: '*Poor adherence is associated with reduced effectiveness, increased morbidity and increased medical costs. Patients prefer once-weekly BPs over daily treatment; however, compliance and persistence remain suboptimal in many patients receiving once-weekly or monthly therapy.*' (pages 38-39)

We note some review articles that discuss adherence to osteoporosis treatment.[14-17] In summary, these articles agree with the claims within the submission that adherence with oral bisphosphonate therapy is sub-optimal, and that increased fracture risk is a consequence of this.

Adherence, Persistence & Compliance – Amgen sponsored study analysing data from the General Practice Research Database (GPRD)

This is reported in section 5.8 and Appendix 9.17, table 9.71.

In summary, the study found that:

- [redacted]
- [redacted]
- [redacted]

As this study reviewed data from the GPRD, IV ibandronate and zoledronic acid were not included, because these are given by IV infusion in hospital. (N.B. GPRD data will under-estimate use of IV BPs.)

Adherence, Persistence & Compliance – Comments

Both the submission and the review articles state that adherence may be improved with less frequent medicine administration. [14,16] If this is the case, it could be hypothesised at quarterly, six-monthly or annual therapy would be associated with improved adherence relative to therapy delivered more frequently.

It is possible that with very infrequent therapy, patients may forget to take it / attend for it. Therefore, call / recall systems may be required.

However a study by Gold and colleagues reported that there was no advantage in terms of adherence between weekly risedronate and monthly ibandronate.[18] Indeed persistence was poorer with the monthly drug. This study was funded by Proctor and Gamble, the manufacturers of risedronate, and two of the three authors work for the company.

Gastrointestinal side-effects are a common reason for patients not adhering to oral bisphosphonate therapy, and that these are unlikely to be age dependent. However, one review article (Kothawala et al) commented that 'elderly patients also encounter more barriers to adherence because they tend to take more medications, long term, with more frequent dosing schedules than younger patients take'.[19]

Therefore, the complexity of multiple drug therapy may mean that elderly patients do not take the drugs as directed, and are therefore at higher risk of gastrointestinal side-effects, leading to lower adherence. As a result, in real life patients eligible for denosumab may differ from people adherent to oral bisphosphonates.

Amgen state that in the base case analysis, persistence has been assumed to be 100% for all treatments (section 6.3.8). This is unlikely in real life but seems reasonable as a starting point. In sensitivity analyses, it appears that persistence for oral therapies is varied (section 6.3.8, pages 202 and 244). However, no mention is made of persistence with denosumab varying (page 177).

Furthermore, the submission also states: '*Zolendronate, ibandronate & teriparatide have been excluded from persistence sensitivity analyses in view of the absence of evidence on the persistence profile of these therapies*' (pg.175). However there is a study of persistence with teriparatide by Ziller and colleagues, though it was probably published too late (15th January 2010) to be included.[20] This study showed quite good persistence, with 79% still taking daily SC injections at 2 months. Adherence was good at 80% (90% by self-reporting but less with medication possession ratio monitoring). The same clinic has 49% adherence for oral BPs and 39% for raloxifene. However it should be noted that raloxifene was being used in a severe group who had an average of four vertebral fractures, in whom better compliance would be expected.

One hundred percent persistence with any therapy is unrealistic, though in the case of denosumab and zoledronate, perfect "compliance" is assured for 6 and 12 months (and perhaps more) after first injection. One review reported that in a hypothetical choice, the majority of patients preferred annual IV zoledronate to frequent oral BPs.[15]

In the sensitivity analyses, poor compliance was assumed to only apply with orally and frequently administered therapies. Because of how it is administered, compliance with denosumab and other treatments given by injection is not really an issue, so this is probably reasonable – if patients receive the medication, they will receive it as intended, in full dose. But persistence may be an issue if patients don not attend. Note that this may be less of an issue with denosumab if patients self-administer, though then there may be a question of recall

Adherence, Persistence & Compliance - Conclusions

It is recognised that adherence with oral bisphosphonate therapy is sub-optimal, and it has been suggested that the development of therapies that require to be given less frequently may help to achieve this. Although some studies support this[14,16] a recent study [18] found no difference when weekly risedronate was compared with monthly ibandronate. Therefore, it can not be necessarily assumed that denosumab administered six-monthly will result in significant improvements in adherence.

Following initial administration of denosumab, both compliance and persistence will be 100% for six months. However, in the longer term persistence with therapy may be less than 100%.

3.3.2 Bone mineral density as predictor of fractures

The risk of fractures increases as BMD falls, with approximately a doubling of risk with each SD reduction. So the risk is roughly doubled at a T-score of -1, four-fold a T-score -2, eightfold at T-score – 3, and so on.

Trials which use fractures as the primary outcomes will require large numbers of patients, because relatively few women have fractures. However, all will have BMD measurements, and if that is used as the primary outcome, the trial will require far fewer recruits, and can report much sooner.

However unlike with T-score and fracture risk, in trials of treatment of osteoporosis, there is less agreement between changes in BMD and fracture risk, and the correlation may vary amongst drugs. Some reviews have examined this issue.

Bruyere and Reginster[21] concluded that:
"*there is limited evidence to support the use of BMD as a reliable indicator of fracture risk reduction with antiresorptive agents"*
by which they meant bisphosphonates and raloxifene. For example, they noted that the reduction in fracture risk with alendronate was much higher than predicted from the increase in BMD. However in the case of strontium, they concluded that there was a stronger relationship, and that BMD could be used for monitoring effect of treatment with strontium.

In a review of the literature, Cefalu noted that the reduction in fracture risk with alendronate was much greater than might be expected from the increase in BDM.[22] He also noted a time difference, based on risedronate trials, in that fracture rates reduced more rapidly than BMD

rose, with the full anti-fracture effect being achieved by one year whereas the full BMD effect took three years. In another alendronate trial, a 10 mg dose had more effect on BMD than a 5 mg dose, but there was no difference in fracture rates.

Cefalu compares raloxifene with the bisphosphonates, noting a similar reduction in vertebral fractures over 3 years, but a smaller rise in BMD with raloxifene. He suggests that we should consider both bone density and bone quality, and that the bisphosphonates may improve bone structure, and hence have an effect additional to BMD.

In a third review, Seeman[23] concluded that;
"*Finding a greater BMD response to one drug than another is not necessarily indicative of a greater risk reduction....*"

In an earlier analysis of 16 published trials, Delmas and Seeman had shown that there was no correlation between changes in BMD and reductions in fracture risk.[24]

In a fourth review, Small[25] came to a similar conclusion;
"*In evaluating the efficacy of treatments in osteoporosis clinical trials, fracture end points are the most relevant, and caution should be used when consulting BMD data only to interpret efficacy*"

Conclusion
Time has not permitted a full review of the validity of BDM as an outcome in trials of osteoporosis treatments, but there is clearly some doubt about the value of BMD, suggesting that fractures should be the principal outcome.

3.4 Equity

Section 3 of the submission notes that no issues relating to equity or equality have been addressed in the submission.

However it might be worth reflecting on the risk of fracture in women who had had a stroke in the past. Some may have problems swallowing or standing to take oral BPs, and they may be a group with more to gain from injectable drugs such as denosumab or zoledronate. They are more likely to have falls. Kerse and colleagues from Auckland found that 37% of stroke survivors had a fall within six months of the stroke, and 8% of those had a fracture.[26]

We have seen a recent statement (unreferenced, in a proposal for an HTA trial) that in the UK 10% of women with hip fractures have had a previous stroke, and making the case for the use of bone restoring drugs in this group, who may lose bone mass through inactivity.

A Swedish study by Ramnemark and colleagues followed 1139 stroke survivors for an average of 3 years.[27] One hundred and twenty patients had fractures, and the risk was higher in women than men; 84% of the fractures were caused by falls, 45% of fractures were hip, 14% wrist, 13% other arm and 9% vertrebral. The risk of any fracture was 4% after 1 year, 15% after 5 years, and 24% after 10 years.

In addition to looking at fractures in patients who had had strokes, the same group looked at the history of strokes in patients presenting with fractures, and found that in two series, in patients over 65 years, 16% and 29% had had previous strokes.

Using Scottish data, Dennis and colleagues estimated that 10.6% of those who had had a stroke, would have a fracture by 10 years.[28] However their denominator was all stroke admissions, and since some would die in the first episode, the percentage of those having subsequent fractures would be higher.

Myint and colleagues reviewed the literature on fracture occurrence and prevention after stroke.[29] They noted that a number of studies had shown marked reduction in BMD in the affected, paretic, side after stroke. The main cause is probably immobility. Over 80% of hip fractures after stroke occur on the hemiparetic side. They cite an RCT of single dose zoledronate after stroke which prevented bone loss, compared to a decrease in BMD in the placebo group. In the study by Poole and colleagues, patients who were unable to walk one week after a stroke were randomised to 4 mg IV zoledronate or placebo.[30] Seventy two percent of them had falls in the first year. Those randomised to zoledronate had no bone loss in the trochnateirc region of the hemiplegic hip, whereas those on placebo had 8% bone loss. On the unaffected side, BMD rose by 1% on zoledronate and fell by almost 3% on placebo. Many were not osteoporotic before the stroke, but there was a high prevalence of vitamin D deficiency.

In summary, women who have had a stroke are at increased risk of falls and fractures, and of bone loss because of reduced mobility. They may also find it more difficult to take oral BPs.

4. CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

No concerns. Given that there was a recent batch of reviews done to support production of the NICE guideline on osteoporosis, Amgen simply updated the evidence base by searching the usual databases (MEDLINE, Embase, and Cochrane) for more recent studies. Our searches did not indicate that they had missed any relevant studies.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The Amgen review started from the inclusion and exclusion criteria used by the NCCNSC reviewers (Table B1 of submission) but also included studies which had only BMD as an outcome. Our view is that such studies are not necessary when we have studies for all the drugs which report fractures. We think the BMD studies should have been excluded. However we do note that the NICE scope (December 2008) included BMD as an outcome, and Amgen can reasonably attribute the inclusion of the BMD studies to NICE.

4.1.3 Details of any relevant studies that were not included in the submission?

No relevant studies, published at the time, were excluded. However the 2-year DIVA trial[13] report was not used in the indirect comparison.

4.1.4 Description and critique of manufacturers approach to validity assessment

No concerns

4.1.5 Description and critique of manufacturers outcome selection

The correct outcomes, clinical fractures were fully reported and used in the economic modelling. Other less relevant outcomes such as BMD and morphometric fractures were reported, and this increased the length of the submission.

4.1.6 Describe and critique the statistical approach used

The main assessment of relative effectiveness comes from the complex indirect comparison. On the whole, we think the methodology seems sound, but the submission is too large for very detailed checking of results.

They have used the "adjusted indirect comparison" method of Bucher. [31] They were only able to include one study comparing denosumab with placebo, although this is large. There was a thorough analysis of heterogeneity assumptions in the meta-analysis in some detail, but for indirect comparisons there is an additional similarity assumption.[32] There was a less transparent approach to considering the effects of differences in the baseline characteristics of the studies. We have summarised these in the appendix.

The issue here is whether a relative risk from, e.g., a 12-month trial (Liu 2004[33]) in Chinese women mean age 65, with BMI 23, should be used in indirect comparison with a 3-year trial in European women with mean age 72, BMI 26.[11] The Amgen submission does not seem to have adequately assessed the similarity of the FREEDOM study to other studies with respect to the factors that could modify relative treatment effect: patient characteristics, setting, methodological quality, etc. Therefore the limitations of the indirect comparison method could have been more clearly stated; i.e. variability in trial characteristics has the potential to cause bias and confounding.

Bucher and colleagues[31] have commented on problems with their methods, noting that;

- It assumes that the size of the treatment effect is constant despite differences in the populations' baseline characteristics.
- Indirect comparison may give a greater effect size than direct comparison, as in their study of HIV drugs. (Conversely, Song and colleagues[32] in a study of smoking cessation, found that a greater effect size in direct than indirect comparison.)
- The quality of studies of one drug may be poorer than another, and poor quality studies tend to over-estimate effect size
- The frequency of outcomes may depend on length of follow-up
- The efficacy of treatment may vary in different subgroups. Treatment might have a greater effect in those more severely affected.

From the Amgen submission subgroups analyses, we note that denosumab is significantly more effective in reducing non-vertebral fractures in women with lower BMI, lower femoral neck T-score, and no previous vertebral fracture. It also has more effect on hip fractures in older women.

The Amgen review team therefore attempted to use meta-regression to investigate whether mean age, BMD, etc. are associated with different treatment effects amongst drugs, but they have included studies from all comparators together, so the benefit of these analyses for any one comparison between denosumab and another treatment is limited. The statistical power of the meta-regression to show significant effects is also relatively low because of the small number of studies.

In some of the tables, the number of included studies in each comparison could have been more clearly stated.

Note that the term "adjusted indirect comparison" in the methods does not use the word adjusted in its usual sense of adjusting results for important predictive variables or confounding factors, but refers to the use of placebo as the common comparator, rather than, say, directly comparing the denosumab arm of one RCT with the strontium arm of another. This is a much safer form of indirect comparison. Comparing one arm from one study with one arm from another study would be like comparing two unrelated case series. The word "adjusted" is not actually used anywhere in the Bucher paper.[31] It is used by Song and colleagues.[32]

Indirect comparisons are used only because there are no direct head to head fracture-outcome trials of denosumab with another active comparator. The main denosumab trial, the FREEDOM study, has been criticised for having the control group of high risk women allocated to only placebo,[34] but Cummings and colleagues point out that both the FDA and the EMEA require placebo-controlled trials of three years duration, so any criticism should be directed at the regulators rather than industry.[11]

4.2 Summary of submitted evidence

4.2.1 Summary of results

The two key elements in the clinical effectiveness evidence submitted, are the FREEDOM trial[11] of denosumab versus placebo, and the indirect comparison with other drugs.

Full details of the FREEDOM trial are given in the Amgen submission, but in brief;

- It was a good quality trial with 7,868 women in 214 centres in many countries and three-year follow-up

- The primary outcome was radiographic fracture, whereas our interest is in clinical fractures. However hip, clinical vertebral, and other fracture rates are reported

- The comparator was placebo, rather than an active one

- Hip fractures rates were reduced from 1.2% in the placebo group to 0.7% in the denosumab group, relative risk (RR) 0.60 (95% CI 0.37 – 0.97).

- Clinical vertebral fractures were reduced from 2.6% in the placebo arm to 0.8% in the denosumab arm, RR 0.31 (95% CI 0.20-0.47)

- The only serious adverse effect reported in the FREEDOM trial was skin infection – 12 patients in the denosumab arm versus one in the control arm. This was statistically significant (p= 0.002) but significance of this event was lost when all the denosumab studies were pooled (i.e. adding those which had BMD as outcome).

The safety of denosumab was thoroughly reviewed by the FDA (August 2009) which had data from approximately 14,000 subjects with up to five years of denosumab exposure. These came partly from trials of other indications for denosumab such as bone loss in breast and prostate cancer. The FDA summary of safety noted that;[3]

- Subjects in the denosumab arm had a slightly higher incidence of serious infections of skin, ear, urinary tract and abdomen, and more non-serious skin infections.

- There was a very slightly greater incidence of some cancers in the denosumab group, especially breast, with 20 (0.5%) of the denosumab group versus 10 (0.3%) of the placebo groups discontinuing due to breast cancer. Such small differences are not statistically significant.

- The FDA did have a concern about bone structure. Biopsies showed suppression of dynamic bone formation parameters which raised a theoretical risk of delayed fracture healing and atypical fracture. Note that there was no difference in delayed fracture healing in the FREEDOM trial, but numbers of cases were very low, two in the denosumab group and four in the placebo arm.

So given current experience, denosumab seems safe.

The indirect comparisons

As stated above, the methodology of this seemed sound.

Table 3 summarises the results of the direct comparison of denosumab and its main comparators with placebo: random effects model (taken from Table B22 of Amgen submission)

Table 3 [redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comparisons which are statistically significant (at the 5% level) are given in bold.

The results for strontium are not too different from the meta-analysis provided for TA 160 which quoted a hip RR of 0.85 and all non-vertebral of 0.84. [1] This similarity provides some confidence in the results from the indirect comparison.

Table 4 is a reduced version of Table B23 of the Amgen submission and gives the results of the indirect comparison of denosumab with the other drugs. RRs less than 1.0 mean that denosumab is more effective.

Table 4 [redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	

RR< 1 favours denosumab. Comparisons which are statistically significant (at the 5% level) are given in bold.

[redacted]

Box 1. [redacted]

[redacted]

[redacted]

It may be worth remembering the compliance issues at this point. In trials, compliance is better than in routine care. We know that adherence and persistence are poor with all the oral agents (see table B28 of Amgen submission, and text above). We do not have persistence data for zoledronate or denosumab yet, but it is likely to be much better (assuming it is supported by a call/recall system in GP or secondary care) than with strontium or raloxifene. Anecdotal evidence from the Aberdeen clinic is that many women prefer an annual infusion to daily or weekly tablets.

In terms of clinical effectiveness, the main comparator to denosumab therefore seems to be zoledronate.

5. ECONOMIC EVALUATION

5.1 Overview

As part of the manufacturer's submission, existing cost-effectiveness evidence for Denosumab was reviewed, and a cost-effectiveness model was developed comparing Denosumab with a range of comparators. The economic analysis focused on the use of Denosumab in women for whom oral bisphosphonates are unsuitable.

5.1.1 Overview of manufacturers review

The manufacturer conducted a systematic review of economic studies assessing the costs and/or cost-effectiveness of denosumab, as described in section 6.1 of their submission. Two modelling studies were identified comparing denosumab to risendronate and no treatment respectively. One study by Strom and colleagues reported incremental cost per QALY ratios of £10,700 and 14,300 for comparisons with risedronate and no treatment respectively.[35] A second study (Hiligsmann and Reginster, 2009) found denosumab to be cost-effective compared with no treatment.[36] The studies were only available in abstract form making it difficult to appraise their quality.

With the focus of the current submission being on the use of Denosumab in women for whom oral bisphosphonates are unsuitable, the risendronate comparison becomes irrelevant, though the comparison with no treatment maybe relevant for groups who do not meet current treatment criteria for alternatives to oral BPs (see blow).

Further Searches of Medline and Embase undertaken by the ERG identified no further cost-effectiveness studies relevant to the current submission.

5.1.2 Overview of manufactures cost-effectiveness model

The de novo economic evaluation focused on the cost-effectiveness of denosumab for: 1) the primary prevention of fragility fractures in women with osteoporosis (T-score ≤ -2.5) who are unable to comply with or tolerate oral BPs; and, 2) the secondary prevention of subsequent fragility fractures in women with osteoporosis and prior fragility fractures who are unable to tolerate oral BPs. A Markov model was used to simulate the transition of cohorts through a series of discrete states, allowing women to experience hip fracture, clinical vertebral fracture,

wrist fracture and other types of fracture on a 6-monthly basis (see section 6.2.2 in manufacturers submission). In the base case analysis fracture risks were estimated based on epidemiological literature; age specific fracture risks were first estimated for women in the general population, before aged matched z-scores were estimated for an osteoporotic cohort (using the NHANES III database) and used to impute age specific relative risks for the different types of fracture (based on available epidemiological literature). An alternative risk estimation algorithm (FRAX® WHO Fracture Risk Assessment Tool) was applied in a sensitivity analysis to estimate fracture risk in cohorts of women at defined T-scores with and without additional independent clinical risk factors for fracture.

Costs and utility losses associated with wrist fractures and other types of fracture were assumed to last for one year, whereas hip fractures and clinical vertebral fractures were modelled to incur ongoing costs and utility losses. A simplifying assumption was made regarding the state transitions allowed in the model; individuals experiencing a vertebral fracture could no longer experience a wrist fracture or other type of fracture (apart from clinical vertebral fractures and hip fractures). After a hip fracture individuals could no longer experience any type of fracture other than a subsequent hip fracture. This is somewhat unrealistic as experience of a hip or vertebral fracture would put individuals at higher risk of further fractures. It was noted that these assumptions worked in favour of less efficacious therapies, and so will favour oral therapies in comparison with denosumab, but also favour denosumab slightly in comparison with zoledronate.

All cause mortality was modelled to increase by varying degrees following different types of fracture. Mortality risks were estimated using available epidemiological literature. Costs associated with alternative fracture types were estimated using hospital episode statistics for England and Wales in conjunction with the Department of Health healthcare resource group (HRG) tariff.[37] The cost-effectiveness of denosumab and its comparators was assessed by superimposing treatment effects and costs on the natural history model. Drug costs were obtained from the British National Formulary (BNF)[38] and treatment effects were derived from a systematic review of randomised controlled trials. Treatment effects were incorporated as the relative risks for the different types of fracture, obtained from an indirect comparison where each treatment was compared with placebo (see Table B22 in manufacturer's submission). Treatment was assumed to continue for 5 years and costs and quality adjusted life years were tracked over the lifetime of the cohorts. For the base case analysis it was assumed that fracture risk would return linearly to baseline levels over the course of one year after discontinuation of treatment. This is a conservative assumption that works on favour of oral therapies, since oral therapies are likely to have poorer compliance

and so may not have such a prolonged treatment offset period. Persistence and compliance were also held at 100% for all therapies in the base case analysis, which again may favour oral therapies in comparison with denosumab, but will not affect comparisons between denosumab and the IV BPs. The impact of alternative assumptions surrounding treatment offset, persistence and compliance were assessed through sensitivity analysis.

5.1.3 Initial clarifications

Following submission of the manufactures report and economic model, the ERG sought clarification on a number of issues relating to the economic evaluation (Table 5). The following section presents a summary and critique of the economic evaluation after consideration of the manufacturer's responses to the initial clarification requests.

Table 5 Initial clarifications sought from the manufacturer

Clarification request	**Response satisfactory?**	**Reviewers comments**
1. Clarity was sought on how/whether base fracture risk estimates update over time in the model (with decreasing BMD or with increasing fracture prevalence).	Yes	Further explanation was provided as to how age matched BMD and fracture incidence were used at baseline to estimate risk of fracture by age. This component of the model is quite difficult to follow but as demonstrated below it generates fracture incidence rates that are generally consistent with those observed in an osteoporotic cohort.
2. Clarity was sought on how risks of fracture below different T-Score cut-offs were estimated, and whether sub-group analysis for different T-scores used "below threshold" risks, or "at threshold risks"?	Yes	It was made clear that analyses using fracture risk estimates derived from the epidemiological literature were conducted for cohorts at or below different T-Score cut-offs.
3. It was noted that relative fracture risks associated with osteoporosis, which are age dependent in the model,	Yes	This represented a minor bug in the model which had very little or no bearing on results. The bug

were not updating with age after 30 years – This only affected the running of the model for groups of younger cohorts of women (i.e. 50 and below).		was corrected and any affected analyses were updated in response
4. It was noted that the relative risk of fracture at a given age depended on the start age of the cohort; i.e. the relative risk for hip fracture (associated with osteporosis) at age 70 varied depending on the start age of the cohort. It was not entirely clear why this was the case.	Yes	As per point 1 above
5. It was noted that the reported model validation validated the structure of the model but not the risk equations used to derive baseline fracture risks. A request was made to assess how well the risk equations predict the three year incidence of fractures observed in the placebo arm of the Freedom trial, when age, T-score, and fracture prevalence were set to match the average characteristics of participants in this trial	Yes	The model performed relatively well in predicting the fracture incidence observed in the placebo arm of the Freedom trial, which provides reassurance that model does not inflate the risk of fracture and therefore overestimate cost-effectiveness of the more efficacious comparators relative to less efficacious ones.
6. It was noted that a switch for allowing estimation of fracture risk at specific T-score thresholds (as opposed to "below threshold") was not functional in the model initially received by the ERG.	Yes	A version of the model was provided with this switch fully functional.
7. It was noted that a switch enabling estimation of fracture risk using the WHO FRAX algorithm was disabled in the version of the model initially received by the ERG	Yes	A fully functional version of the FRAX algorithm was provided subject to confidentiality agreement.
8. Clarity was sought on how the relative risks of mortality were derived	Yes	Clearer explanation was provided in relation to how and why

and how they were applied in conjunction with the base mortality risks to estimate mortality following fractures		downward adjustments were made to the relative risks of mortality following different types of fracture.
9. Reassurance was sought regarding the generalisability of the utility multipliers used in the model? - i.e. were these multipliers derived from populations of similar age with similar likelihood of admission to nursing homes following hip fracture etc.	Yes	Reassurance was provided that the utility multipliers were obtained from cohorts of women similar to the modelled cohorts.
10. When estimating costs of fracture, HRG costs were inflated (using excess bed day costs) in some instances to account for the longer than average length of stay observed for women matching the age of the modelled cohort? Clarity was sought on the assumptions that were applied when doing this.	Yes	Further explanation of the rational underlying this assumption was provided. It seems justifiable on the grounds that elderly osteoporotic fracture patients tend to incur longer than average hospital stays.

5.2. Summary and critical appraisal of the manufactures de novo economic evaluation

A summary and critique of the economic evaluation is provided under the subheadings below.

5.2.1 Cohort details

The base case analysis was conducted for two separate cohorts: 1) 70 year old women with a T-score of -2.5 or below with no prior fragility fracture; and 2) 70 year old women with a T-score of -2.5 or below with a prior fragility fracture. Further subgroup analysis was undertaken for different T-Score cut-offs within different age groups. A sensitivity analysis was also conducted to assess cost-effectiveness by the presence/absence of additional independent clinical risk factors for fracture in 70 year old women, with and without prior fragility fractures. The approach of using fracture risks at or below different T-score

thresholds made it difficult to gauge how the cost-effectiveness of denosumab might vary across T-score bands within age groups i.e. the approach that was used to inform previous NICE guidance (T160, T161). [1,2] For this reason the ERG requested some additional subgroup analysis using at threshold risks for cohorts with different T-scores.

5.2.2 The comparators

Primary comparators included strontium renelate, raloxefene, and no treatment. These were selected on the basis of current NICE treatment guidance for women with osteoporosis unable to comply with or tolerate oral BPs. However, NICE does not currently recommend raloxefene for primary prevention of osteoporotic fractures (on grounds of cost-effectiveness), and it only recommends the use of strontium renelate for primary prevention in certain subgroups (defined by age, T-score and presence absence of independent clinical risk factors). Strontium renelate and raloxefene are recommended for secondary prevention in certain subgroups, again based age, T-score and presence/absence of independent clinical risk factors. Therefore, the appropriate treatment comparator, according to NICE guidance, varies for different subgroups contained within the modelled cohorts (Table 6).

Secondary comparators considered by Amgen were intravenous (IV) ibandronate, IV zoledronate and teriparatide. These were selected as secondary comparators on the grounds that they do not represent current practice in the UK, and are limited to use in secondary care settings. In addition, the point was made that NICE has not issued any guidance on IV ibandronate or IV zoledronate. However, clinical opinion sought by the ERG suggests these drugs are currently considered at the same time denosumab will potentially be considered (i.e. in women for whom oral BPs are unsuitable). Furthermore, it is a questionable assumption that denosumab will be administered in a primary care setting, so for these reasons the ERG considered IV ibandronate and IV zoledronate to be relevant comparators.

Comparisons with the oral BPs were also included in the manufacture's model, though given the focus on treating women unable to adhere to oral BPs, these were considered largely irrelevant for this appraisal. However, the findings of these comparisons are summarised briefly in the results section.

Table 6 Appropriate comparators for densoumab by prior fracture status, age, T-score and clinical risk (based on current nice guidelines for those unable to tolerate oral BPs)

	Number of independent clinical risk factors		
No prior fragility fracture	**0**	**1**	**2**
Age 65-69 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	No treatment
-3.5	No treatment	No treatment	No treatment
-4	No treatment	No treatment	Strontium
-4.5	No treatment	Strontium	Strontium
Age 70-74 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	No treatment
-3.5	No treatment	No treatment	Strontium
-4	No treatment	Strontium	Strontium
-4.5	Strontium	Strontium	Strontium
Age >=75 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	Strontium
-3.5	No treatment	No treatment	Strontium
-4	Strontium	Strontium	Strontium
-4.5	Strontium	Strontium	Strontium
Prior fragility fracture			
Age 50-54 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	No treatment
-3.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
-4	No treatment	Strontium/raloxefine	Strontium/raloxefine
-4.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
Age 55-59 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	No treatment
-3.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
-4	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine

Age 60-64 (T-scores)			
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	No treatment
-3.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
-4	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
Age 65-69 (T-scores)	0	1	2
-2.5	No treatment	No treatment	No treatment
-3	No treatment	No treatment	Strontium/raloxefine
-3.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
-4	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
Age 70-74 (T-scores)			
-2.5	No treatment	No treatment	Strontium/raloxefine
-3	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-3.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
Age >=75 (T-scores)			
-2.5	No treatment	Strontium/raloxefine	Strontium/raloxefine
-3	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-3.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine
-4.5	Strontium/raloxefine	Strontium/raloxefine	Strontium/raloxefine

5.2.3 Natural history

An eight-state Markov model, with a 6-month cycle length, was used to model the natural history of cohorts of women (section 6.2.2 of manufacturer's submission). Fracture risk estimates for women with osteoporosis were estimated by applying age specific relative risks (based on age specific BMD z-scores) to fracture risks for the general population. Further adjustments were made for the increased risk of fracture associated with prior fragility fracture. For the base case analysis and subgroup analysis presented in the original

submission, age specific fracture risk estimates were calculated for all women at or below specific T-score thresholds. This was done by dividing the T-score distribution (below the threshold) into 0.1SD wide slices, and estimating the relative risk attributable to each T-score slice. The average risk below different T-score thresholds was estimated by taking the weighted average risk across all T-score slices below the threshold (based on the proportions of the cohort in each slice). As stated in the manufacturer's submission, this approach is preferable to using the average T-score below a threshold to estimate risk, since fracture risk increases exponentially as T-score declines. Therefore, the average fracture risk in the population is found in individuals with a below average T-score.

Patients in the model could remain well or experience a hip fracture, vertebral fracture, wrist fracture or other type of osteoporotic fracture on a 6-monthly basis. When a fracture was sustained, patients were modelled to remain in the appropriate fracture state for two stages (1 year). Following this period patients with wrist fractures or other types of fracture were modelled to return to the well state, while those with vertebral fractures or hip fractures were modelled to enter a post fracture state. Patients in the post vertebral fracture state could then no longer incur a wrist fracture or other type of osteoporotic fracture (other than a subsequent vertebral fracture or hip fracture), while those in the post hip fracture state could only incur further hip fractures. This simplifying assumption may slightly bias comparisons in favour of less efficacious therapies, since prevention of hip and vertebral fracture means more patients remain at risk of wrist and other types of fracture.

[redacted]

Treatment costs and quality of life decrements associated with wrist or other types of fracture were modelled to last one year, while clinical vertebral fractures and hip fractures were modelled to incur ongoing costs and quality of life losses. Patients also experienced an increased risk of mortality following fracture, determined by relative risks for all cause mortality obtained from a review of the literature.

Treatment effects and costs were superimposed on this natural history model to estimate the net costs and health benefits associated with the alternative comparators over the lifetime of the modelled cohort. Health benefits were measured and valued in quality adjusted life years (QALYs), with QALY gains for alternative treatments capturing improved survival and maintenance of health status over time.

5.2.4 Mortality

The model accounted for observed increases in the risk of mortality following fracture, by applying relative risks for mortality obtained from a review of the literature. An increased risk was modelled for the first and subsequent years post hip and vertebral fracture. For other types of fracture, subjects were modelled to be at increased risk of mortality for one year only. The relative risks for mortality following all types of fracture were adjusted downwards to account for the observation that a significant proportion of mortality following fracture can be explained by co-morbidity. An assumption was made that 30% of all mortality following all fracture types is causally related, which is consistent with similar assumptions employed in previous economic analyses conducted for NICE.

5.2.5 Treatment effects

Treatment was modelled to continue over a period of 5 years by applying relative risks to the estimated baseline risks of fracture in the osteoporotic cohort. Following the termination of treatment after 5 years, an assumption was made that patients would return linearly to baseline risk levels over a period of one year.

The relative risks associated with alternative drug treatments were taken from a random effects meta-analysis model where each drug treatment was compared directly with a common comparator (placebo). Where there was no evidence relating to the effects of interventions on clinical vertebral fractures, it was assumed that effects for this outcome would be the same as for morphometric vertebral fractures. Where there was no evidence for the effects of interventions on the risk of hip and/or wrist fracture, a relative risk of one was assumed. Since there was no consistent definition for other types of fracture across studies, a relative risk of one was assumed for all interventions (including denosumab).

Based on the above assumptions zoledronate was modelled (due to absence of evidence) to have no effect on wrist fractures or other types of fracture, while denosumab was modelled to reduce the risk of wrist fracture by 15.8%.

[redacted], and examination of the Horizon trial results[12] suggests it may also have some efficacy for prevention of other types of fracture which have not been counted in the manufacturer's model.

[redacted]

[redacted]. It was felt therefore that these assumptions could bias the comparison between denosumab and zoledronate, and for this reason the ERG requested further sensitivity analysis where the effect of denosumab and zoledronate on wrist fracture were equalised.

5.2.6 Resources and costs

Costs included in the model were drug treatment and administration costs, fracture costs, and costs associated with selected adverse events.

Costs associated with fractures were estimated using hospital episode statistics in conjunction with the department of health HRG tariff (Department of Health, 2006).[37,39] Assumptions surrounding the percentage of patients treated in hospital, with and without surgery, for the different fracture types were informed by a combination of expert opinion, review of literature and analysis of routine data. For example, to estimate the proportion of vertebral fractures treated in hospital, the number of hospital episodes for vertebral fracture were divided by the projected fracture incidence in the population. Hospital episode statistics were further used to estimate the proportion of hospital inpatients treated as day cases and long stay. The HRG costs for fracture events were adjusted when the age specific length of stay relating to an event was more than 2 days above the mean length of stay for the corresponding HRG. This was done to reflect the fact that fracture costs in elderly osteoporotic women are above population averages. Methods and assumptions used for estimating fracture costs seem reasonable and were well justified.

Drug costs for the comparators were obtained from the British National Formulary, and a number of assumptions were employed when estimating administration and monitoring costs for the alternatives. The most questionable assumption related to the administration costs for denosumab. The manufacturer assumed that denosumab would be initiated and administered entirely in primary care, requiring two GP visits per year (one for delivery of the first dose, and the second for monitoring and delivery of the second dose). Clinical opinion sought by the ERG suggests that it is unlikely that GPs will agree to deliver denosumab as part of

General Medical Services (GMS) activity, if at all. The manufacturer conducted a sensitivity analysis to assess the impact of delivering one dose of denosumab in secondary care per year, but for this scenario it was assumed that the second dose would be delivered during a GP visit. The manufacturer also conducted a sensitivity analysis to demonstrate the impact on findings of patients self administering one of the denosumab doses each year, with the other being given during an annual GP monitoring visit. The ERG felt the latter scenario was unrealistic since the injection is required so infrequently.

If denosumab were to be administered in primary care, it is still likely that patients would require an annual review in secondary care, and it is also likely that GPs would demand an enhanced service payment for the delivery of this specialist service. The average unit costs of the routine GP visits may, or may not, accurately reflect the true opportunity cost to trusts of implementing this service. The ERG requested some additional sensitivity analysis to assess more fully the impact of varying denosumab administration costs in line with the above delivery models. In response the manufacturer argued that:

> *"Regardless of whether an enhanced service payment would be considered appropriate for the delivery of denosumab in primary care, there is no case for a change to the cost inputs in the model. It is important to distinguish between the costs of resources which are directly utilised in providing denosumab and the funding arrangements for primary care. The model fully accounts for the former – with respect to primary care, this is covered by the acquisition cost of denosumab and the cost of the GP visit to administer the injection. Even if the delivery of denosumab in primary care became an enhanced service, the resource costs incurred by the NHS in providing it to a given patient would remain unchanged to those in the model. The enhanced service arrangements would be used as an additional income stream into general practice but would not alter the resource costs of delivering the service to a patient. Therefore, to include the fee provided to general practice for any enhanced service as an <u>additional</u> cost in the model would be inappropriate"*

Clinical opinion sought by the ERG suggested that if denosumab were to be initiated and administered in secondary care, it would require an annual review to check bone markers and vitamin D status as well as an outpatient/day case appointment to administer the drug. In the best case scenario one of the doses could be given during the annual review visit, thus retaining the need for only two appointments per year. Clinical opinion also suggests that the manufacturer may have underestimated the costs associated with zoledronate, as they assumed that monitoring for these patients would be undertaken in primary care rather than

secondary care. Given these uncertainties, the ERG requested further sensitivity analysis and also undertook further sensitivity analysis on denosumab and zoledronate administration/monitoring costs using the manufacturer's model (see Section 6).

It should be noted that in response to the request for sensitivity analysis to assess the impact of assuming initiation of denosumab in secondary care, with more intensive follow-up, the manufacturer argued that there is no regulatory stipulation for denosumab to be administered in the secondary care setting or under specialist advice only:

"The European Medicines Agency (EMEA) was sufficiently assured of the clinical efficacy and safety of denosumab to place no restrictions on the care setting for denosumab draft SPC"

The manufacturer went on to state that

"Given that denosumab would be less costly and therefore more cost-effective when administered in primary care; and that there are no restrictions in the denosumab draft SPC in respect of care setting, we would anticipate that recommendations be made to encourage the administration of denosumab in a primary care setting in order to ensure the most efficient use of NHS resources".

Regarding the request for more sensitivity analysis to reflect the possibility that denosumab patients will require more intensive follow-up (to assess bone turnover marker estimation), the manufacturer stated that the "draft SPF contains no requirements or recommendations for BTM estimation".

Costs associated with selected adverse events were also incorporated in the manufacturer's model (gastrointestinal adverse events associated with oral therapies and cellulitus associated with denosumab). Other types of adverse events associated with denosumab and its comparators were excluded (e.g. other skin infections (denosumab); osteonecrosis of the jaw (zoledronate). Given the marginal difference between denosumab and zoledronate in terms of efficacy and, possibly, treatment costs, differences in the safety profile of these two alternatives could influence relative cost-effectiveness.

5.2.7 Health related quality of life

Utility decrements associated with fracture were applied to population norms in the form of utility multipliers. These were obtained from a systematic review of the literature. The

authors justified the omission of utility values obtained directly from the denosumab trial participants on the basis that there were relatively few fracture events in the trial and the trial design precluded the assessment of health status immediately after fracture events. No statistically significant difference in HRQOL was observed between the denosumab and placebo arms of the FREEDOM trial (section 6.4.3 of manufacturer's submission).

Appraisal of the manufacturer's quality of life review methodology and the primary studies included in the review suggests that suitable utility multipliers have been applied in the model. However, it should be noted that many of the multipliers were derived from observational time series studies without independent control groups. Thus they do not control for all potential confounding factors. Another point worth noting is the assumption that utility loss relative to population norms remains at a constant rate in the second and subsequent years post hip and vertebral fracture. This assumption may slightly overestimate utility loss associated hip and vertebral fracture if the observed trend towards improved quality of life in the second year post fracture were to continue in subsequent years.

Utility loss associated with hip and vertebral fracture was modelled in a two stage process, with a larger decrement in the first year following fracture and an ongoing but less severe utility penalty in subsequent years. Utility multipliers for the first and subsequent years following hip fracture were obtained from a meta-analysis of studies utilising the EQ-5D responses.[40]

Utility loss associated with clinical vertebral fracture was estimated separately for the proportion of patients managed in hospital and the proportion managed in primary care. Hospitalised patients were assumed to incur decrements derived from the EQ-5D scores of a predominantly hospitalised cohort.[41] Non-hospitalised patients were assumed to incur decrements obtained from cohorts with prevalent morphometric fractures.[42,43] The manufacturer's submission makes the point that these multipliers may underestimate the utility loss associated with clinical vertebral fractures managed in primary care.

Utility multipliers associated with wrist fracture were also obtained from the literature and applied in the model for one year following the event.[41] Due to an absence of evidence, the same multiplier and the same approach were also used to model utility loss associated with other types of fracture.

Finally, utility decrements associated with the selected adverse events mentioned above were also included in the model. The relative safety profiles of denosumab and zoledroante, and

their potential impacts on HRQOL, may prove important if the two options are found to have similar administration costs. .

5.2.8. Sensitivity analysis

The manufacturer conducted fairly extensive deterministic sensitivity analysis and also undertook probabilistic sensitivity analysis. Important variables and assumptions that were not originally subjected to sufficient sensitivity analysis, as previously flagged, were: 1) assumptions surrounding different drug administration scenarios, and 2) uncertainty surrounding the effect of alternative drugs on wrist fractures and other types of fracture. Requests for further sensitivity analysis were made by the ERG as detailed below.

PSA was undertaken, though it should be noted that the distributions assigned to the administration cost parameters will be based on the manufacture's original costing assumptions. If these are thought to be inappropriate the PSA will require updating. A potentially important omission from the PSA is the underlying fracture risk estimates. As stated by the manufacturer, data limitations meant that distributions could not be estimated for these parameters. As a result the acceptability curves may overestimate the probability of denosumab being considered cost-effective at different willingness to pay thresholds. Deterministic sensitivity analysis shows the cost-effectiveness findings to be sensitive to underlying fracture risk.

5.2.9 Model validation

The manufacturer presented model validation in the form of: 1) a comparison with a published osteoporosis model; 2) a comparison between the simulated and actual fracture risk observed for the Swedish general population; 3) a model rebuild using a microsimulation approach (Treeage Pro 2008); 4) a review of the model by an independent analyst; and 5) a reproduction of the results of the FREEDOM trial.[11] The model generally performed well in the validations (see section 6.8 of the manufacturer's original submission). It was noted by the ERG that although the reproduction of the FREEDOM trial validated the structure of the model, it did not validate the risk equations used to generate baseline risks in the osteoporotic population. A request was therefore made to the manufacturer to demonstrate how well the risk equations could predict the three year incidence of fractures observed in the placebo arm of the FREEDOM trial (when age, T-score, and fracture prevalence were set to match the average characteristics of participants in the Freedom trial). The response from the

manufacturer showed that the model produced a projected three year fracture incidence comparable with that reported in the placebo arm of the FREEDOM trial.

5.2.10 Summary of strengths and weaknesses

The comprehensive validated model was used to assess the cost-effectiveness of denosumab against all potential comparators. The main weaknesses and concerns, as highlighted in the preceeding sections, relate to the assumptions surrounding the administration and monitoring costs for denosumab and its comparators, and the relative effectiveness of denonsumab and zoledronate for the prevention of wrist fractures and other types of fracture. Additional concerns relate to the manner in which sub-group analysis was conducted, which made it difficult to ascertain how cost-effectiveness varied across T-score bands. A structured appraisal of the submission is provided in Table 7 using the 10-point checklist of Drummond and colleagues,[44] and the submission is compared with the NICE reference case in Table 8 .

Given the concerns identified, a request was made for the following additional analysis to be undertaken by the manufacturer:

- Further sensitivity analysis using more conservative assumptions for the cost of administering denosumab in a primay care setting (i.e. initiation in secondary care with changes to GP costs to reflect the possible impact of GPs demanding enhanced service payments and patients requiring more intensive follow-up).
- Further sub-group analysis presenting results by age, risk factors, and T-score bands (e.g. -2.5 to -3), rather than results below T-score thresholds.
- A sensitivity analysis assuming that zoledronate has the same effect as deonsumab on wrist fractures.

The manufacturers responses to these requests are presented and summarised in section 5.3.2

Table 7 Structured appraisal of the manufacture's economic evaluation

Item	Critical appraisal	Reviewers comment
Was a well defined question posed in answerable form?	Yes	The economic analysis aimed to assess the cost effectiveness of Denosumab versus a range of comparators from the health service perspective (incorporating costs of health and social care). The focus was on treatment of women with osteoporosis who could not tolerate/adhere to oral BPs. Separate analyses were conducted for those with and without a prior fragility fracture.
Was a comprehensive description of competing alternatives given?	Yes	A large number of comparators were included and no appropriate comparator was omitted. Some of the comparators were considered irrelevant given the focus on women who are unable to tolerate /adhere to oral BPs (see text for details). A reasonable description of alternatives was provided, though limited detail was provided on the level of monitoring and follow-up that would be required with the alternative pharmaceutical agents.
Were all important and relevant costs and consequences for each alternative identified?	?	Assumptions surrounding the cost estimates for denosumab, and some of the comparators, seem inappropriate. The main issue relates to the level of monitoring and follow-up required for denosumab. The manufacturer assumed administration/monitoring costs for denosumab of two GP visits per year, with a BMD scan once every two years. It is the view of the ERG that this may underestimate the costs of denosumab (see text for details). Costs and consequences associated with adverse events were also given limited attention.
Were costs and consequences measured accurately in appropriate physical units?	?	Numbers of fractures were counted in the model and justified assumptions were made regarding the proportion of patients that would be treated in hospital (with and without surgery) for the different types of fracture. Drug doses were measured in appropriate units, though as mentioned above, assumptions surrounding the number of GP/hospital visits required for

		administration and follow-up with denosumab are questionable.
Were costs and consequences valued credibly?	Yes	Appropriate unit costs were used to value resource use, and appropriate utility multipliers were used to value time spent in adverse health states. Limited consideration was give to costs and consequences associated with treatment related adverse events.
Were costs and consequences adjusted for differential timing?	Yes	Future costs and quality adjusted life years were appropriately discounted at 3.5% per annum.
Was an incremental analysis of alternatives performed?	Yes	Denosumb was compared incrementally with all comparators. However, the relevance of incremental comparison with raloxifene is limited give the lack of cost-effectiveness of this treatment compared with no treatment. The relevant comparator varies depending on the T-score and risk profile of the cohort. Thus it is incremental analysis by subgroup that provides the most useful information.
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic and probabilistic sensitivity analysis was performed. Of particular interest were the analyses where costs of denosumab were increased to assume administration in a secondary care outpatient clinic (this may represent a more likely cost scenario for denosumab). However, the effects of this change on the comparison with iv ibandronate and iv zoledronate were not clearly reported. The manufactures did not assess the impact of more optimistic assumptions for the effect of zoledronate on wrist fractures. A further issue of concern was the approach used to conduct subgroup analyses. Most results were obtained using risks at or below alternative T-Score cut-offs rather than risks within T-Score bands. The latter approach is required to assess cost-effectiveness across different subgroups of women.
Did the presentation and discussion of study results include all issues of concern to the users?	No	The conclusions are difficult to assess given the above uncertainties. Also, the appropriate comparator varies by subgroup making it difficult to come to a general

		conclusion on the cost-effectivness of denosumab.

Table 8 Comparison of manufacturer's economic evaluation with the NICE reference case

Attribute	**Reference case**	**Submission conforms?**	**Comment on whether or not the de novo evaluation meets the NICE reference case**
Comparators	Alternative therapies including those routinely used in NHS	Yes	All relevant comparators were included, though the relevance of some is questionable. In addition, drugs classed as secondary comparators may be highly relevant for this submission (IV ibandronate and IV zolendronate).
Perspective - costs	NHS and PSS	Yes	Includes health care costs and PSS costs associated with nursing home care following hip fracture
Perspective - benefits	All health effects on individuals	Yes	An adequate number of health states have been included to capture the health consequences of fracture. A question remains as to how fuller consideration of adverse events might influence the comparison between denosumab and zolendronate, which have very similar efficacy and possibly similar administration costs.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	A lifetime horizon was employed.
Synthesis of evidence	Literature review and indirect comparisons	Yes	Clinical effectiveness data for the comparators comes from a review of RCTs and an indirect comparison where each alternative was compared with Placebo. Evidence for most comparators comes from a single study. The evidence for IV ibandronate was obtained from a trial of oral ibandronate given lack of evidence at time of modelling. Assumptions surrounding the relative effect of alternative treatments on

			wrist fractures and other types of fracture may bias certain comparisons (see text for details).
Outcome measure	QALYs	Yes	QALYs were estimated by applying utility multipliers associated with different types of fracture and adverse events, to EQ-5D population norm. The multipliers were derived via a review of studies assessing EQ-5D responses (scored using the UK general population tariff) before and after different types of fracture.
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	The EQ-5D descriptive system was used capture health status in the studies from which utility multipliers were derived.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	The UK EQ-5D time trade-off (TTO) scoring tariff was used in the studies from which utility multipliers were derived.
Source of preference data	Sample of public	Yes	Representative sample of UK general population.
Discount rate	Health benefits and costs	Yes	A discount rate of 3.5% per annum was applied to future costs and benefits. Alternative rates were assessed through deterministic sensitivity analysis
Equity	No special weighting	Yes	No weighting of QALYs was undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	PSA was undertaken though the central tendency for certain distributions may bias the acceptability curves in favour of denosumab (denosumab administration costs, effect of zoledronate on wrist fracture).

5.3. Summary and interpretation of the manufactures economic evaluation results

5.3.1 Summary of manufacturers base case results

The results of the manufacturers base case results are reproduced in Table 9 and Table 10.

These analyses represent cost-effectiveness findings for cohorts of 70 year old women with a T-Score at or below -2.5, with and without a prior fragility fracture.

Table 9 Primary comparisons: base-case cost-effectiveness for denosumab, strontium, raloxifene and no treatment

				vs. lowest cost comparator			**ICER vs. low-cost comparator**		**ICER for comparison with Denosumab[a]**	
	LYs	**QALY**	**Cost**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LYs**	**QALYs**	**LYs**	**QALYs**
No prior fracture										
No Treatment	11.606	7.991	9,455	0.000	0.000	0	—	—	47,220	29,223
Raloxifene[b]	11.628	8.009	10,764	0.022	0.018	1,310	60,786	74,239	26,383	9,289
Denosumab	11.642	8.048	11,135	0.036	0.057	1,680	47,220	29,223	—	—
Strontium	11.622	8.007	11,138	0.016	0.016	1,684	104,069	102,592	Denosu-mab dominant	Denosu-mab dominant
Prior fracture										
No Treatment	11.492	7.797	12,060	0.000	0.000	0	—	—	17,719	12,381
Raloxifene	11.548	7.852	13,410	0.056	0.055	1,351	24,021	24,524	4,820	2,046
Denosumab	11.576	7.917	13,543	0.084	0.120	1,483	17,719	12,381	—	—
Strontium	11.531	7.841	13,698	0.039	0.044	1,638	41,767	37,123	Denosu-mab dominant	Denosu-mab dominant

[a] Pairwise ICERs for denosumab versus each strategy are presented to demonstrate the cost-effectiveness of denosumab relative to the existing guidance recommendations in TA160 and TA161.

[b] Raloxifene is not recommended by NICE in patients with no prior fracture.

Table 10 Secondary comparisons: base-case cost-effectiveness for denosumab, ibandronate iv, zoledronate iv and teriparatide

				vs. lowest cost comparator			ICER vs. low-cost comparator	
	LYs	**QALYs**	**Costs**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LYs**	**QALYs**
No prior fracture								
Denosumab	11.642	8.048	11,135	0.000	0.000	0	—	—
Zoledronate (iv)	11.646	8.053	11,490	0.004	0.005	355	88,386	70,900
Ibandronate (iv)	11.624	8.011	13,890	–0.017	–0.037	2,756	Denosumab	Denosumab
Teriparatide**	11.648	8.066	24,710	0.007	0.018	13,576	2,073,082	772,424
Prior fracture								
Denosumab	11.576	7.917	13,543	0.000	0.000	0	—	—
Zoledronate (iv)	11.586	7.930	13,903	0.010	0.012	360	34,292	29,029
Ibandronate (iv)	11.540	7.849	16,526	–0.036	–0.068	2,984	Denosumab	Denosumab
Teriparatide	11.584	7.947	26,867	0.008	0.030	13,324	1,580,601	451,269

ICERs compared with denosumab are not presented separately, as denosumab is the lowest cost treatment in this scenario

**Teriparatide is not recommended by NICE in patients with no prior fracture. NICE have not appraised ibandronate iv or zoledronate iv.

The manufacturers base case results suggest that for 70 year old women with no prior fracture, denosomab dominates strontium, is highly cost-effective compared with raloxifene, and is borderline cost-effective compared with no treatment. The slightly more efficacious drugs (zoledronate and teriparatide) have unfavourable incremental cost effectiveness ratios compared to denosumab in these women.

In women with a prior fragility fracture, the cost-effectiveness of denosumab versus the primary comparators (no treatment, raloxifene and strontium) increases. In these women the slightly more efficacious zoledronate reaches borderline cost-effectiveness compared with densumab.

5.3.2 Interpretation of manufacturers base case results

The difficulty with the base case analysis is that cost-effectiveness will vary substantially within subgroups within the cohorts. Furthermore, the appropriate comparator will also vary by subgroup according to existing NICE guidance (Table 6). The base case analysis also relies on the manufacturers original assumptions surrounding the cost of administering denosumab. If this turns out to underestimate the true cost of delivery, the ICERs will become less favourable for denosumab.

An additional point to note is that neither raloxifene nor strontium compare very favourably with no treatment; ICERs £74,239 and £102,529 per QALY respectively for women with no prior fragility fracture, and £24,524 and £37,123 per QALY respectively for women with a prior fragility fracture. These findings are consistent with previous NICE guidance (TA160 and TA161) which only recommend strontium and raloxifene for certain subgroups. T161 does not recommend raloxifene for the primary prevention of fragility fractures and, for 70 year old women, only recommends the use of strontium for primary prevention in high risk subgroups; i.e. those with T-score <= -4.5 with no additional risk factors, those with t-score <= -4 with 1 independent clinical risk factor, and those with a T-score <= -3.5 with two independent clinical risk factors. T160 does however does recommend the use of raloxifene and strontium for most subgroups of 70 year old women contained within the prior fragility fracture cohort (except those with a T-score between -2.5 and -3, with fewer than 2 independent clinical risk factors)

For the above reasons the demonstrated high cost-effectiveness of denosumab compared with raloxifene and strontium needs to be interpreted with caution. Compared with no treatment, the cost-effectiveness of denosumab is borderline for women with no prior fragility fracture (£29,223 per QALY) although better for women with a prior fragility fracture (£12,381 per QALY).

Moving onto the secondary comparators, the comparison between denosumab and zoledronate is clouded by uncertainty relating to costs of administering these two drugs, and also uncertainty relating to their relative efficacy for the prevention of wrist fracture. The key issue in this comparison is how much less costly denosumab administration and monitoring will actually work out to be in practice compared with zoeldronate administration and monitoring.

A further point worth mentioning is that if denosumab can be delivered within the costs assigned by the manufacturer, additional comparisons with oral BPs suggest that it may be a cost-effective option for patients who fail to tolerate alendronate; ICER £21,189 versus risedronate and £8,680 versus oral Ibandronate in the lower risk cohort (70 year old women with no prior fragility fracture). Therefore, for those failing to tolerate oral alendronate, it might be considered more cost-effective to offer denosumab as opposed risedronate and or oral Ibandronate.

5.3.2 Summary of the manufacturer's sensitivity analysis results

The manufacturer provided tables of deterministic sensitivity analysis results in their original submission (section 6.7.7.). These showed that alterations to most key parameters had limited impact on comparisons between denosumab and raloxifene, strontium and no treatment. The impact of sensitivity analysis on comparisons with IV ibandronate, IV zoledronate and tereparatide were presented in appendices (appendix 15). The findings were most sensitive to changes in cost assumptions for administration of denosumab.

The manufacturer provided an analysis where the cost of administering denosumab was increased to assess how cost-effectiveness would change if it were delivered in secondary care. For this analysis a cost of £127 per year was applied for one orthopaedic outpatient attendance per year. The manufacturer noted that this reflects the cost of a first attendance and so may overestimate attendance costs in subsequent years. Administration of the second dose was assumed to occur in general practice.

Under this scenario, the cost per QALY for denosumab versus no treatment rose to £36,185 in those with no prior fragility fracture, and £15,720 in those with a prior fragility fracture. However, this change leads to zoledronate dominating denosumab in women with and without a prior fragility fractures.

In response to further requests from the ERG, the manufacturer undertook a further sensitivity analysis in which it was assumed that denosumab would be initiated in secondary care and thereafter be delivered in a GP setting. This had less impact on the comparison with zoledronate, with the ICER for zoledronate versus densomab being £52,976 per QALY and £21,788 per QALY for women without and with prior fragility fractures respectively. However, it took the ICER for comparison with no treatment slightly over £30,000 per QALY in women with no prior fragility fracture.

In response to the ERG request to assess the impact of varying GP costs to reflect the possibility of enhanced service payments being required, the manufacturer argued that all GP resource use had been appropriately valued through application of the average unit cost per GP visit (see section 5.2.6)

This argument appears to be based on the assumption that the unit cost for two GP visits per patient will accurately reflect the opportunity cost (per patient) to trusts of getting GPs to agree to administer denosumab to osteoporosis patients. This may or may not be the case.

Another point of contention was the assumed efficacy of denosumab for prevention of wrist fractures and the assumed lack of efficacy of zoledronate for prevention of wrist fracture. An additional analysis was requested whereby efficacy of denosumab and zoledronate were set to be equal. In response the manaufacturer pointed out that it would be inappropriate to assign zoledronte the demonstrated efficacy of denosumab for prevention of wrist fracture, as the indirect treatment comparison showed that some drugs could have similar efficacy at one site, yet very different efficacy at another site. However, the manufacturer's indirect comparison showed that while denosumab and zoledronate have very similar efficacy for prevention of hip fracture, zoledronate has if anything a slightly higher efficacy for prevention of non-vertebral fractures; i.e the category which includes hip fractures, wrist fractures and other types of clinical fracture. Therefore, it seems reasonable to run an analysis where there is no difference between the two drugs for prevention of wrist fracture. This analysis showed that the cost-effectiveness of zoledronate versus denosumab improved from £70,900 to £60,687 per QALY in women without a prior fracture, and from £29,029 to £25,202 per QALY in women with a prior fracture (with manufacturer's original costing assumptions held constant).

The PSA results show denosumab to have ~50% probability of being considered cost-effective at WTP threshold of £30,000 per QALY compared with the primary comparators (in 70 year old women with a T-score at or below -2.5 and no prior fracture). The corresponding probability increases to ~90% in women with a prior fragility fracture. PSA comparisons for denosumab with zoledronate, IV ibandronate, teriparatide were presented in appendices. They showed probabilities of ~0.7 and ~0.6 for denosumab being considered cost-effective at a WTP threshold of £30,000 per QALY (in 70 year old women with and without prior fragility fractures respectively). These probabilities are all dependent on the manufacturer's initial costing assumptions.

5.3.3 Interpretation of the manufacturer's sensitivity analysis results

The manufacturer's sensitivity analysis demonstrates that the cost-effectiveness findings for denosumab are sensitive to the assumed costs of administering the drug. Under the secondary care assumptions, zoledronate becomes dominant over denosumab.

The ICER for zoledronate versus denosumab also appears to be moderately sensitive to assumptions regarding the relative efficacy of the two drugs for the prevention wrist fractures.

The PSA suggests that denosumab has only a 50% probability of being considered cost-effective at WTP threshold of £30,000 per QALY in 70 year old women without prior fragility fracture, and ~90% chance of being considered cost-effective in women with a prior fragility fracture. It should be noted that these results are based on cost distributions centred on the manufacturers initial admin/monitoring cost estimates, which may be overly optimistic. In addition, the PSA does not incorporate uncertainty relating to uncertainty in the underlying risk of fracture in the osteoporotic cohort.

5.3.4 Summary of the manufacturer's sub-group analysis results

The manufacturer provided more detailed subgroup analysis in response to a request from the ERG. Subgroup analysis in the original submission only demonstrated how cost-effectiveness varied using different treatment cut-offs (e.g. all women with a T-sore "at or below" -2.5, -3, -3.5 and so on), making it difficult to ascertain how cost-effectiveness changed across groups of patients in different T-score bands (see section 6.9 of manufacturer's original submission). Therefore a request was made to provide results showing ICERs by bands of both age and T-score. The ERG asked the manufacturer to use predicted risks at the central point in T-score bands to represent the average risk within the band (e.g. risk at – 2.75 to model the average risk for individuals in T-score band -2.5 to -2.99).

The manufacturer provided the additional analyses but urged caution when interpreting the results, giving the reason that using average T-score to represent risk within bands may underestimate the average fracture risk within the band. This is because risk increases exponentially with respect to declining T-score. So for example, a patient with a T-score of -2.75 will not have the mean risk of fracture for patients within the T-score band -2.5 to -3; Depending on the distribution of patients across all T-scores contained within each band, the average risk may be found at a T-score lower, or higher, than the central T-score. Therefore there will be a degree of inaccuracy when using central T-score points to estimate cost-

effectiveness for women within T-score bands. Caution has been exercised when interpreting the additional subgroup analysis tables.

Results of the subgroup analysis are reproduced in Table 11, Table 12, Table 13, and Table 14 for the primary and secondary comparators respectively. Table 11 and Table 13 present results for women with no prior fragility fracture, and Table 12 and Table 14 present results for women with prior fragility fractures. It should be noted that all ICERs reflect initial costing assumptions – i.e. only 2 GP visits per year for denosumab administration and monitoring costs, and one GP visit per year for zoledronate monitoring. The ICERs in bold type mark the appropriate comparisons for the different subgroups based on existing NICE guidance.

Further subgroup analysis was also provided for a cohort of women aged 70 years, using the FRAX algorithm. This shows how cost-effectiveness varies by T-score and the presence/absence of independent clinical risk factors for fracture. The findings have been reproduced in Table 15, Table 16, Table 17 and Table 18 for the primary and secondary comparators respectively. Note again that these analyses rely on original base case assumptions regarding the cost of denosumab administration. The appropriate ICERs, according to current NICE guidance, have been marked in bold type.

5.3.5 Interpretation of the manufacturer's sub-group analysis results

The results presented in Table 11 and Table 12 suggest that denosumab should not be considered cost-effective compared with the primary comparators in women below the age of 73 with a T-score >= -2.75 and no prior fragility fracture, or in women below the age of 63 with a T-score >= to -3.25 and no prior fragility fractures. Cost-effectiveness improves as age increases and T-score decreases, and with the presence of prior fragility fracture(s) (i.e. as fracture risk increases).

The analysis undertaken using the FRAX algorithm demonstrates that the presence of independent clinical risk factors, particularly rheumatoid arthritis, also improves the cost-effectiveness of denosumab vesus the primary comparators. It should also be noted that all the factors that increase the base risk of fracture, and hence the cost-effectiveness of denosumab versus cheaper less effective therapies, also increase the cost-effectiveness of zoledronate versus denosumab. The choice between denosumab and zoledronate for different subgroups will be sensitive to changes in the relative cost of administering and monitoring the two drugs.

It should be noted again that Table 11 to Table 18 present subgroup analysis using the manufacturer's costing assumptions, and assumptions regarding the relative efficacy of denosumab and zoledronate for the prevention of wrist fracture. If the appraisal committee find these assumptions to be unrealistic, further subgroup analysis will be required.

Table 11 Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (no prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
-2.75	58	12.074	12.052	12.053	12.049	10,638	10,424	9,954	8,613	9,672	32,905	**81,254**	No Treat	3
-2.75	63	10.451	10.427	10.428	10.422	10,649	10,467	10,012	8,680	7,475	27,385	**67,886**	No Treat	2
-2.75	68	8.778	8.742	8.744	8.728	10,589	10,513	10,105	8,786	2,091	14,090	**36,211**	No Treat	2
-2.75	73	7.160	7.125	7.125	7.114	10,247	10,278	9,913	8,636	Domt	9,540	**34,800**	No Treat	2
-2.75	78	5.650	5.619	5.616	5.611	9,537	9,872	9,633	8,420	Domt	Domt	**28,686**	Dmab	1
-3.25	58	11.936	11.907	11.907	11.900	13,955	13,798	13,353	12,005	5,416	21,122	**54,449**	No Treat	2
-3.25	63	10.324	10.292	10.292	10.283	13,937	13,822	13,398	12,058	3,575	16,928	**45,838**	No Treat	2
-3.25	68	8.669	8.620	8.621	8.599	13,818	13,863	13,511	12,176	Domt	6,392	**23,746**	Dmab	1
-3.25	73	7.076	7.029	7.027	7.011	13,309	13,506	13,211	11,923	Domt	2,008	**21,436**	Dmab	1
-3.25	78	5.588	5.547	5.542	5.535	12,328	12,938	12,808	11,590	**Domt**	Domt	13,722	Dmab	1
-3.75	58	11.750	11.710	11.709	11.698	18,596	18,531	18,127	16,770	1,650	11,582	**35,577**	No Treat	2
-3.75	63	10.153	10.111	10.109	10.096	18,506	18,498	18,122	16,769	179	8,632	**30,261**	No Treat	2
-3.75	68	8.522	8.456	8.454	8.427	18,273	18,504	18,239	16,879	Domt	506	**14,732**	Dmab	1
-3.75	73	6.964	6.901	6.896	6.875	17,490	17,936	17,749	16,442	**Domt**	Domt	11,783	Dmab	1
-3.75	78	5.507	5.453	5.445	5.434	16,114	17,109	17,130	15,903	**Domt**	Domt	2,893	Dmab	1
-4.25	58	11.508	11.454	11.449	11.435	25,070	25,157	24,820	23,447	Domt	4,294	**22,266**	Dmab	1
-4.25	63	9.933	9.875	9.871	9.854	24,826	24,987	24,686	23,314	Domt	2,240	**19,137**	Dmab	1
-4.25	68	8.331	8.244	8.237	8.205	24,375	24,894	24,760	23,366	**Domt**	Domt	7,989	Dmab	1
-4.25	73	6.818	6.734	6.725	6.699	23,140	23,960	23,935	22,599	**Domt**	Domt	4,517	Dmab	1
-4.25	78	5.402	5.332	5.319	5.306	21,181	22,705	22,934	21,692	**Domt**	Domt	Domt	Dmab	1

NMHB, Net Monetary Health Benefit; ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161; N.B. N.B. Caution should be exercised when interpreting these analyses as using at threshold T-score at the central point in the band may underestimate the mean fracture risk in the band

Table 12 Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (prior fracture – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
-2.75	58	11.808	11.757	11.762	11.733	13,693	13,634	13,232	11,876	1,164	10,111	**24,374**	Dmab	1
-2.75	63	10.239	10.189	10.196	10.165	13,330	13,269	12,873	11,521	1,241	10,594	**24,600**	Dmab	1
-2.75	68	8.629	8.559	8.571	8.519	12,979	13,035	12,702	11,346	Domt	4,775	**14,853**	Dmab	1
-2.75	73	7.075	7.016	7.022	6.985	12,263	12,427	12,128	10,832	**Domt**	**2,582**	15,993	Dmab	1
-2.75	78	5.606	5.563	5.562	5.545	11,121	11,619	11,445	10,230	**Domt**	**Domt**	14,619	Dmab	1
-3.25	58	11.588	11.520	11.523	11.486	18,271	18,370	18,040	16,665	Domt	3,546	**15,820**	Dmab	1
-3.25	63	10.050	9.985	9.991	9.953	17,619	17,696	17,367	15,992	Domt	4,214	**16,662**	Dmab	1
-3.25	68	8.475	8.385	8.396	8.332	17,023	17,268	17,036	15,637	**Domt**	**Domt**	9,706	Dmab	1
-3.25	73	6.965	6.887	6.893	6.846	15,957	16,346	16,156	14,825	**Domt**	**Domt**	9,541	Dmab	1
-3.25	78	5.532	5.475	5.472	5.450	14,380	15,213	15,178	13,945	**Domt**	**Domt**	5,349	Dmab	1
-3.75	58	11.308	11.217	11.216	11.172	24,769	25,129	24,915	23,515	**Domt**	**Domt**	9,241	Dmab	1
-3.75	63	9.812	9.728	9.730	9.685	23,612	23,911	23,687	22,281	**Domt**	**Domt**	10,500	Dmab	1
-3.75	68	8.278	8.162	8.171	8.098	22,593	23,137	23,056	21,604	**Domt**	**Domt**	5,495	Dmab	1
-3.75	73	6.822	6.722	6.724	6.669	20,963	21,694	21,667	20,289	**Domt**	**Domt**	4,395	Dmab	1
-3.75	78	5.435	5.361	5.356	5.329	18,756	20,051	20,208	18,950	**Domt**	**Domt**	Domt	Dmab	1
-4.25	58	10.968	10.848	10.840	10.791	34,031	34,816	34,785	33,352	**Domt**	**Domt**	3,836	Dmab	1
-4.25	63	9.524	9.417	9.414	9.364	31,991	32,645	32,580	31,138	**Domt**	**Domt**	5,345	Dmab	1
-4.25	68	8.034	7.891	7.895	7.816	30,240	31,256	31,397	29,891	**Domt**	**Domt**	1,603	Dmab	1
-4.25	73	6.643	6.515	6.513	6.451	27,691	28,941	29,157	27,720	**Domt**	**Domt**	Domt	Dmab	1
-4.25	78	5.313	5.220	5.211	5.179	24,557	26,481	26,897	25,606	**Domt**	**Domt**	Domt	Dmab	1

NMHB, Net Monetary Health Benefit

ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161.

N.B. Caution should be exercised when interpreting these analyses as using at threshold T-score at the central point in the band may underestimate the mean fracture risk in the band

Table 13 Subgroup analysis: secondary comparison: denosumab, ibandronate, zoledronate and teriparatide (no prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Highest NMHB	Position for Dmab
-2.75	58	12.07	12.06	12.08	12.08	10,638	13,167	11,005	24,885	Domt	167,417	7,430,561	Dmab	1
-2.75	63	10.45	10.43	10.45	10.46	10,649	13,200	11,015	24,742	Domt	147,541	3,269,486	Dmab	1
-2.75	68	8.78	8.75	8.78	8.79	10,589	13,254	10,948	24,371	Domt	80,582	1,110,914	Dmab	1
-2.75	73	7.16	7.13	7.16	7.18	10,247	12,990	10,594	23,576	Domt	91,581	880,223	Dmab	1
-2.75	78	5.65	5.62	5.65	5.67	9,537	12,584	9,851	21,938	Domt	115,546	716,224	Dmab	1
-3.25	58	11.94	11.91	11.94	11.94	13,955	16,564	14,324	28,116	Domt	124,335	1,733,113	Dmab	1
-3.25	63	10.32	10.30	10.33	10.34	13,937	16,584	14,305	27,926	Domt	110,422	1,239,521	Dmab	1
-3.25	68	8.67	8.62	8.67	8.69	13,818	16,657	14,178	27,421	Domt	60,644	577,059	Dmab	1
-3.25	73	7.08	7.03	7.08	7.10	13,309	16,285	13,654	26,404	Domt	67,570	489,197	Dmab	1
-3.25	78	5.59	5.55	5.59	5.62	12,328	15,757	12,632	24,356	Domt	82,832	428,561	Dmab	1
-3.75	58	11.75	11.71	11.75	11.77	18,596	21,337	18,966	32,619	Domt	92,677	769,761	Dmab	1
-3.75	63	10.15	10.11	10.16	10.18	18,506	21,306	18,876	32,335	Domt	83,436	629,820	Dmab	1
-3.75	68	8.52	8.46	8.53	8.56	18,273	21,380	18,632	31,602	Domt	46,117	331,504	Dmab	1
-3.75	73	6.96	6.90	6.97	7.01	17,490	20,818	17,830	30,233	Domt	50,070	291,205	Dmab	1
-3.75	78	5.51	5.45	5.51	5.55	16,114	20,076	16,402	27,615	Domt	59,123	267,822	Dmab	1
-4.25	58	11.51	11.45	11.51	11.54	25,070	28,027	25,439	38,875	Domt	69,453	408,204	Dmab	1
-4.25	63	9.93	9.87	9.94	9.97	24,826	27,867	25,195	38,408	Domt	63,856	360,855	Dmab	1
-4.25	68	8.33	8.24	8.34	8.39	24,375	27,894	24,729	37,287	Domt	35,528	202,057	Dmab	1
-4.25	73	6.82	6.73	6.83	6.89	23,140	26,997	23,470	35,355	Domt	37,230	180,352	Dmab	1
-4.25	78	5.40	5.32	5.41	5.47	21,181	25,873	21,447	31,950	Domt	41,779	171,199	Dmab	1

NMHB, Net Monetary Health Benefit; No ICER estimates are provided in bold as teriparatide is not recommended by NICE in TA161 and the other interventions have not been appraised by NICE. N.B. Caution should be exercised when interpreting these analyses as using at threshold T-score at the central point in the band may underestimate the mean fracture risk in the band

Table 14 Subgroup analysis: secondary comparison: denosumab, ibandronate, zoledronate, and teriparatide (prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Highest NMHB	Position for Dmab
-2.75	58	11.81	11.76	11.82	11.83	13,693	16,442	14,059	27,717	Domt	51,145	802,789	Dmab	1
-2.75	63	10.24	10.20	10.25	10.25	13,330	16,057	13,699	27,237	Domt	50,970	895,438	Dmab	1
-2.75	68	8.63	8.57	8.64	8.65	12,979	15,843	13,343	26,541	Domt	31,567	578,134	Dmab	1
-2.75	73	7.07	7.02	7.08	7.10	12,263	15,199	12,613	25,384	Domt	39,764	551,420	Dmab	1
-2.75	78	5.61	5.56	5.61	5.63	11,121	14,394	11,432	23,294	Domt	60,673	526,438	Dmab	1
-3.25	58	11.59	11.52	11.60	11.62	18,271	21,246	18,635	32,066	Domt	39,545	413,171	Dmab	1
-3.25	63	10.05	9.99	10.06	10.08	17,619	20,547	17,988	31,315	Domt	40,210	477,770	Dmab	1
-3.25	68	8.48	8.39	8.49	8.52	17,023	20,168	17,389	30,288	Domt	25,124	329,566	Zoled (iv)	2
-3.25	73	6.96	6.89	6.98	7.00	15,957	19,219	16,306	28,739	Domt	30,708	322,800	Dmab	1
-3.25	78	5.53	5.47	5.54	5.57	14,380	18,121	14,680	26,085	Domt	44,793	323,486	Dmab	1
-3.75	58	11.31	11.22	11.32	11.37	24,769	28,116	25,129	38,195	Domt	30,818	233,942	Dmab	1
-3.75	63	9.81	9.73	9.82	9.86	23,612	26,860	23,980	36,980	Domt	32,246	280,680	Dmab	1
-3.75	68	8.28	8.16	8.30	8.34	22,593	26,176	22,959	35,404	Domt	20,405	200,420	Zoled (iv)	2
-3.75	73	6.82	6.72	6.84	6.88	20,963	24,719	21,308	33,239	Domt	23,999	198,203	Zoled (iv)	2
-3.75	78	5.43	5.36	5.44	5.49	18,756	23,143	19,040	29,806	Domt	33,024	205,128	Dmab	1
-4.25	58	10.97	10.84	10.98	11.06	34,031	37,979	34,377	46,863	Domt	24,082	139,863	Zoled (iv)	2
-4.25	63	9.52	9.41	9.54	9.60	31,991	35,745	32,352	44,852	Domt	26,212	174,687	Zoled (iv)	2
-4.25	68	8.03	7.89	8.05	8.13	30,240	34,504	30,599	42,357	Domt	16,870	127,251	Zoled (iv)	2
-4.25	73	6.64	6.51	6.66	6.73	27,691	32,193	28,026	39,210	Domt	18,920	125,095	Zoled (iv)	2
-4.25	78	5.31	5.21	5.32	5.39	24,557	29,822	24,817	34,704	Domt	24,136	131,826	Zoled (iv)	2

NMHB, Net Monetary Health Benefit; N.B. Teriparatide is recommended in patients who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures. N.B. Caution should be exercised when interpreting these analyses as using at threshold T-score at the central point in the band may underestimate the mean fracture risk in the band

Table 15 Sensitivity analyses (base-case run on FRAX®): primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
No prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	3.80%	14.23%	8.36	8.33	8.33	8.32	8,079	7,950	7,517	6,216	4,631	21,878	**51,271**
–2.75	4.86%	16.00%	8.26	8.23	8.23	8.22	9,107	9,019	8,603	7,300	2,823	16,921	**43,344**
–3	6.20%	18.04%	8.16	8.12	8.13	8.11	10,334	10,296	9,903	8,596	1,077	12,420	**36,240**
–3.25	7.90%	20.43%	8.05	8.01	8.01	8.00	11,795	11,819	11,453	10,143	Domt	8,389	**29,900**
–3.5	10.03%	23.20%	7.93	7.89	7.89	7.87	13,529	13,630	13,298	11,982	Domt	4,818	**24,263**
–3.75	12.68%	26.42%	7.81	7.76	7.75	7.73	15,579	15,775	15,484	14,163	Domt	1,670	**19,260**
–4	15.97%	30.14%	7.67	7.61	7.61	7.59	17,992	18,306	18,066	16,737	Domt	Domt	**14,818**
No prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	7.96%	22.98%	8.22	8.18	8.18	8.16	12,828	12,845	12,482	11,154	Domt	8,255	**27,841**
–2.75	10.12%	25.88%	8.11	8.06	8.06	8.04	14,679	14,771	14,442	13,107	Domt	4,814	**22,846**
–3	12.80%	29.21%	7.98	7.92	7.92	7.90	16,861	17,046	16,759	15,415	Domt	1,764	**18,361**
–3.25	16.12%	33.03%	7.84	7.78	7.77	7.75	19,423	19,724	19,487	18,134	Domt	Domt	**14,329**
–3.5	20.17%	37.36%	7.70	7.62	7.62	7.59	22,422	22,864	22,690	21,325	Domt	Domt	**10,689**
–3.75	25.06%	42.24%	7.54	7.46	7.45	7.42	25,917	26,533	26,436	25,057	Domt	Domt	**7,373**
–4	30.83%	47.64%	7.37	7.28	7.26	7.24	29,973	30,803	30,798	29,405	**Domt**	Domt	4,308
No prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	5.36%	18.37%	8.30	8.27	8.27	8.26	10,056	9,983	9,577	8,264	2,122	14,848	**37,974**
–2.75	6.83%	20.63%	8.20	8.16	8.16	8.14	11,415	11,395	11,014	9,696	505	10,663	**31,826**
–3	8.69%	23.25%	8.08	8.04	8.04	8.02	13,028	13,074	12,722	11,399	Domt	6,920	**26,306**

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
–3.25	11.02%	26.27%	7.96	7.91	7.91	7.89	14,934	15,063	14,748	13,418	Domt	3,599	**21,362**
–3.5	13.92%	29.74%	7.83	7.78	7.77	7.75	17,181	17,411	17,141	15,802	Domt	661	**16,936**
–3.75	17.50%	33.72%	7.69	7.63	7.62	7.60	19,818	20,174	19,958	18,610	Domt	Domt	**12,967**
–4	21.84%	38.24%	7.54	7.47	7.46	7.44	22,902	23,411	23,263	21,903	**Domt**	Domt	9,388
No prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	11.12%	29.30%	8.13	8.08	8.08	8.05	16,209	16,324	16,014	14,658	Domt	3,672	**20,246**
–2.75	14.05%	32.88%	8.00	7.94	7.94	7.91	18,595	18,808	18,544	17,176	Domt	823	**16,280**
–3	17.65%	36.93%	7.86	7.79	7.79	7.76	21,390	21,725	21,516	20,135	Domt	Domt	**12,676**
–3.25	22.04%	41.49%	7.71	7.63	7.62	7.59	24,652	25,136	24,996	23,600	Domt	Domt	**9,380**
–3.5	27.28%	46.54%	7.55	7.46	7.45	7.42	28,445	29,115	29,056	27,644	**Domt**	Domt	6,329
–3.75	33.43%	52.06%	7.37	7.27	7.26	7.23	32,836	33,734	33,775	32,345	**Domt**	Domt	3,454
–4	40.44%	57.93%	7.19	7.08	7.06	7.03	37,892	39,070	39,231	37,784	**Domt**	Domt	677

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table 16 Sensitivity analyses (base-case run on FRAX®): primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
Prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	5.82%	22.09%	8.27	8.23	8.24	8.22	11,110	11,045	10,651	9,320	1,669	13,049	**32,239**
–2.75	7.42%	24.62%	8.16	8.12	8.12	8.10	12,572	12,562	12,195	10,856	236	9,229	**27,248**
–3	9.43%	27.49%	8.05	8.00	8.00	7.98	14,299	14,356	14,022	12,674	**Domt**	**5,800**	22,715
–3.25	11.95%	30.77%	7.92	7.87	7.87	7.84	16,332	16,473	16,178	14,819	**Domt**	**2,739**	18,601
–3.5	15.06%	34.48%	7.79	7.73	7.73	7.70	18,718	18,964	18,717	17,346	**Domt**	**10**	14,862
–3.75	18.89%	38.67%	7.65	7.58	7.57	7.54	21,510	21,885	21,698	20,311	**Domt**	**Domt**	11,450
–4	23.51%	43.35%	7.50	7.41	7.41	7.38	24,766	25,299	25,185	23,782	**Domt**	**Domt**	8,312
Prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	12.05%	34.37%	8.09	8.03	8.03	8.00	17,765	17,882	17,598	16,198	Domt	2,911	**17,804**
–2.75	15.20%	38.17%	7.95	7.89	7.89	7.85	20,295	20,512	20,277	18,861	Domt	267	**14,468**
–3	19.06%	42.41%	7.81	7.73	7.73	7.70	23,249	23,591	23,415	21,981	**Domt**	**Domt**	11,381
–3.25	23.73%	47.09%	7.65	7.57	7.56	7.53	26,689	27,184	27,081	25,627	**Domt**	**Domt**	8,497
–3.5	29.28%	52.17%	7.49	7.39	7.38	7.35	30,681	31,366	31,351	29,875	**Domt**	**Domt**	5,766
–3.75	35.74%	57.60%	7.31	7.20	7.19	7.16	35,292	36,214	36,305	34,808	**Domt**	**Domt**	3,123
–4	43.03%	63.25%	7.12	7.00	6.99	6.95	40,589	41,803	42,022	40,504	**Domt**	**Domt**	496
Prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	8.17%	28.04%	8.19	8.15	8.15	8.12	13,914	13,916	13,566	12,203	Domt	7,837	**24,189**
–2.75	10.37%	31.16%	8.07	8.02	8.02	7.99	15,809	15,882	15,568	14,192	Domt	4,657	**20,235**
–3	13.12%	34.67%	7.95	7.88	7.89	7.86	18,033	18,195	17,924	16,533	**Domt**	**1,807**	16,613
–3.25	16.51%	38.61%	7.81	7.74	7.74	7.71	20,637	20,908	20,690	19,283	**Domt**	**Domt**	13,286

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
–3.5	20.65%	43.00%	7.66	7.58	7.58	7.55	23,675	24,082	23,929	22,503	**Domt**	**Domt**	10,211
–3.75	25.63%	47.84%	7.50	7.41	7.41	7.37	27,210	27,785	27,710	26,265	**Domt**	**Domt**	7,337
–4	31.50%	53.09%	7.33	7.24	7.22	7.19	31,306	32,090	32,108	30,643	**Domt**	**Domt**	4,609
Prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	16.65%	42.66%	7.97	7.89	7.89	7.86	22,363	22,595	22,393	20,928	**Domt**	**Domt**	13,139
–2.75	20.83%	47.06%	7.82	7.74	7.73	7.70	25,572	25,934	25,797	24,308	**Domt**	**Domt**	10,350
–3	25.86%	51.85%	7.66	7.57	7.56	7.52	29,300	29,824	29,766	28,253	**Domt**	**Domt**	7,701
–3.25	31.79%	56.96%	7.49	7.39	7.38	7.34	33,619	34,344	34,380	32,844	**Domt**	**Domt**	5,143
–3.5	38.60%	62.31%	7.31	7.19	7.18	7.14	38,597	39,573	39,723	38,163	**Domt**	**Domt**	2,612
–3.75	46.20%	67.75%	7.11	6.99	6.97	6.93	44,297	45,586	45,873	44,292	**Domt**	**Domt**	31
–4	54.33%	73.08%	6.91	6.77	6.75	6.71	50,762	52,440	52,890	51,292	**Domt**	**Domt**	Domt

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table 17 Sensitivity analyses (base-case run on FRAX®): secondary comparisons: cost-effectiveness results for denosumab, ibandronate (iv), zoledronate (iv) and teriparatide

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
No prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	3.80%	14.23%	8.36	8.34	8.36	8.37	8,079	10,656	8,435	21,890	Domt	106,885	2,154,892
–2.75	4.86%	16.00%	8.26	8.24	8.27	8.27	9,107	11,738	9,463	22,847	Domt	96,568	1,394,014
–3	6.20%	18.04%	8.16	8.13	8.16	8.17	10,334	13,033	10,690	23,988	Domt	87,084	965,755
–3.25	7.90%	20.43%	8.05	8.01	8.06	8.07	11,795	14,580	12,150	25,346	Domt	78,386	697,652
–3.5	10.03%	23.20%	7.93	7.89	7.94	7.96	13,529	16,420	13,883	26,956	Domt	70,424	518,383
–3.75	12.68%	26.42%	7.81	7.75	7.81	7.84	15,579	18,601	15,931	28,857	Domt	63,153	393,083
–4	15.97%	30.14%	7.67	7.61	7.68	7.72	17,992	21,177	18,341	31,089	Domt	56,522	302,686
No prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	7.96%	22.98%	8.22	8.19	8.23	8.24	12,828	15,615	13,193	26,397	Domt	71,445	697,092
–2.75	10.12%	25.88%	8.11	8.06	8.11	8.13	14,679	17,570	15,044	28,124	Domt	64,765	518,777
–3	12.80%	29.21%	7.98	7.92	7.98	8.01	16,861	19,882	17,225	30,158	Domt	58,645	393,994
–3.25	16.12%	33.03%	7.84	7.78	7.85	7.88	19,423	22,605	19,787	32,541	Domt	53,042	303,863
–3.5	20.17%	37.36%	7.70	7.62	7.70	7.75	22,422	25,802	22,783	35,323	Domt	47,910	237,188
–3.75	25.06%	42.24%	7.54	7.45	7.55	7.61	25,917	29,541	26,274	38,556	Domt	43,203	186,924
–4	30.83%	47.64%	7.37	7.26	7.38	7.45	29,973	33,896	30,324	42,295	Domt	38,868	148,431
No prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	5.36%	18.37%	8.30	8.27	8.31	8.31	10,056	12,713	10,417	23,768	Domt	85,685	1,204,768
–2.75	6.83%	20.63%	8.20	8.16	8.20	8.21	11,415	14,145	11,777	25,036	Domt	77,649	850,461
–3	8.69%	23.25%	8.08	8.04	8.09	8.11	13,028	15,850	13,390	26,538	Domt	70,273	622,153
–3.25	11.02%	26.27%	7.96	7.91	7.97	7.99	14,934	17,870	15,296	28,312	Domt	63,515	466,536
–3.5	13.92%	29.74%	7.83	7.77	7.84	7.87	17,181	20,258	17,541	30,399	Domt	57,330	356,272
–3.75	17.50%	33.72%	7.69	7.62	7.70	7.74	19,818	23,070	20,176	32,843	Domt	51,673	275,899
–4	21.84%	38.24%	7.54	7.46	7.55	7.60	22,902	26,368	23,256	35,693	Domt	46,499	216,028
No prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	11.12%	29.30%	8.13	8.08	8.14	8.16	16,209	19,142	16,585	29,602	Domt	58,800	467,724
–2.75	14.05%	32.88%	8.00	7.94	8.01	8.04	18,595	21,666	18,971	31,829	Domt	53,616	357,742
–3	17.65%	36.93%	7.86	7.79	7.87	7.91	21,390	24,632	21,765	34,431	Domt	48,857	277,479
–3.25	22.04%	41.49%	7.71	7.62	7.72	7.77	24,652	28,105	25,025	37,461	Domt	44,484	217,613

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
–3.5	27.28%	46.54%	7.55	7.45	7.55	7.62	28,445	32,158	28,815	40,973	Domt	40,450	172,167
–3.75	33.43%	52.06%	7.37	7.26	7.38	7.46	32,836	36,869	33,200	45,026	Domt	36,706	137,149
–4	40.44%	57.93%	7.19	7.06	7.20	7.29	37,892	42,317	38,247	49,671	Domt	33,191	109,794

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table 18 Sensitivity analyses (base-case run on FRAX®): secondary comparisons: cost-effectiveness results for denosumab, ibandronate (iv), zoledronate (iv) and teriparatide

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
Prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	5.82%	22.09%	8.27	8.24	8.28	8.29	11,110	13,784	11,483	24,773	Domt	72,761	1,079,651
–2.75	7.42%	24.62%	8.16	8.13	8.17	8.18	12,572	15,323	12,947	26,138	Domt	66,532	771,954
–3	9.43%	27.49%	8.05	8.00	8.05	8.07	14,299	17,145	14,675	27,747	Domt	60,810	569,754
–3.25	11.95%	30.77%	7.92	7.87	7.93	7.96	16,332	19,296	16,709	29,639	Domt	55,558	430,075
–3.5	15.06%	34.48%	7.79	7.73	7.80	7.83	18,718	21,829	19,095	31,855	Domt	50,737	330,133
–3.75	18.89%	38.67%	7.65	7.57	7.66	7.70	21,510	24,803	21,887	34,443	Domt	46,309	256,734
–4	23.51%	43.35%	7.50	7.41	7.50	7.56	24,766	28,282	25,140	37,451	Domt	42,236	201,723
Prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	12.05%	34.37%	8.09	8.03	8.10	8.12	17,765	20,718	18,161	31,081	Domt	51,941	432,179
–2.75	15.20%	38.17%	7.95	7.89	7.96	7.99	20,295	23,391	20,693	33,442	Domt	47,939	332,288
–3	19.06%	42.41%	7.81	7.73	7.82	7.86	23,249	26,522	23,649	36,193	Domt	44,256	258,836
–3.25	23.73%	47.09%	7.65	7.56	7.66	7.72	26,689	30,181	27,089	39,388	Domt	40,857	203,711
–3.5	29.28%	52.17%	7.49	7.38	7.50	7.57	30,681	34,443	31,078	43,084	Domt	37,701	161,643
–3.75	35.74%	57.60%	7.31	7.19	7.32	7.41	35,292	39,388	35,686	47,338	Domt	34,743	129,069
–4	43.03%	63.25%	7.12	6.99	7.14	7.24	40,589	45,095	40,976	52,202	Domt	31,923	103,502
Prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	8.17%	28.04%	8.19	8.15	8.20	8.21	13,914	16,693	14,300	27,434	Domt	60,240	687,811
–2.75	10.37%	31.16%	8.07	8.02	8.08	8.10	15,809	18,690	16,198	29,204	Domt	55,425	512,789
–3	13.12%	34.67%	7.95	7.89	7.95	7.98	18,033	21,039	18,424	31,277	Domt	51,002	390,053
–3.25	16.51%	38.61%	7.81	7.74	7.82	7.85	20,637	23,799	21,029	33,699	Domt	46,937	301,245
–3.5	20.65%	43.00%	7.66	7.58	7.67	7.72	23,675	27,030	24,067	36,518	Domt	43,196	235,446
–3.75	25.63%	47.84%	7.50	7.41	7.51	7.57	27,210	30,803	27,601	39,789	Domt	39,739	185,771
–4	31.50%	53.09%	7.33	7.22	7.35	7.42	31,306	35,194	31,694	43,567	Domt	36,525	147,675
Prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	16.65%	42.66%	7.97	7.89	7.98	8.01	22,363	25,502	22,781	35,430	Domt	44,838	303,814
–2.75	20.83%	47.06%	7.82	7.73	7.83	7.87	25,572	28,898	25,992	38,422	Domt	41,748	237,860
–3	25.86%	51.85%	7.66	7.56	7.67	7.73	29,300	32,858	29,722	41,889	Domt	38,887	187,995

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
–3.25	31.79%	56.96%	7.49	7.38	7.50	7.57	33,619	37,464	34,040	45,891	Domt	36,218	149,693
–3.5	38.60%	62.31%	7.31	7.18	7.32	7.41	38,597	42,798	39,014	50,487	Domt	33,692	119,856
–3.75	46.20%	67.75%	7.11	6.97	7.13	7.23	44,297	48,938	44,708	55,726	Domt	31,246	96,295
–4	54.33%	73.08%	6.91	6.75	6.92	7.05	50,762	55,946	51,160	61,631	Domt	28,796	77,421

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

5.4 Summary of the uncertainties and issues

The manufacturer's submission shows denosumab to be a highly efficacious drug for the prevention of fragility fractures in post menopausal osteoporotic women. However, uncertainty relating to the cost of administering the drug, relative to the cost of administering its comparators, prevents a definitive conclusion on its cost-effectiveness. The ERG is of the opinion that the costing assumptions for denosumab may be overly optimistic. If this is the case the reported incremental cost-effectiveness ratios will be overly optimistic.

The comparison with IV zoledronate is particularly sensitive to changes in the relative cost of administering denosumab. This is due to the fact that zoledronate is marginally more costly and more effective than denosumab. The manufacturer suggests that denosumab has a higher efficacy for the prevention of wrist fractures than zoledronate, but this seems questionable in light of the results of their indirect comparison.

The cost-effectiveness of denosumab improves dramatically with factors that increase the baseline risk of fracture (compared with less costly and less effective alternatives). However, these factors also tend to increase the cost-effectiveness of zoledronate compared with denosumab. Given the similar efficacy, and possibly cost, of these two alternatives, it may prove difficult to separate them on grounds of cost-effectiveness. A closer consideration of the relative safety profile of these drugs may prove useful in this case.

6. ADDITIONAL WORK UNDERTAKEN BY THE ERG

Since greatest uncertainty relates to the cost of administering denosumab and zoledronate, the ERG undertook further sensitivity analysis on these costs.

6.1 Sensitivity analysis for alternative secondary care costing assumptions

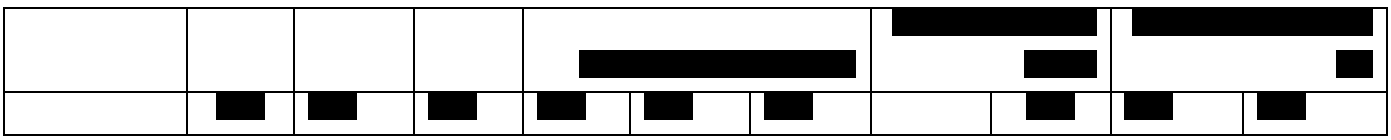
Opinion sought by the ERG suggested that it is far from certain that denosumab will be administered in a primary care setting, and so some analysis was undertaken based on assumptions that denosumab, zoledronate and ibandronate are administered entirely in a secondary care setting.

For this scenario we assigned denosumab costs for two rheumatology outpatient appointments per year (£128 (Department of Health, 2010)), one for delivery of the first dose and a second for monitoring and delivery of the second dose. For zoledronate we costed one outpatient rheumatology appointment per year for monitoring purposes (£128) and one appointment for an infusion as per the manufacturer's estimate (£163.80). An outpatient appointment for monitoring was also included on top of the costs of administering IV ibandronate and teriparatide. No GP costs were included for any of the secondary comparators under this scenario and the cost of biannual DXA scanning were removed (assumed covered by outpatient unit costs).

Table 19 and Table 20 show the cost-effectiveness results under this scenario. Denosumab remains cost-effective compared with raloxifene and strontium, but only remains cost-effective compared with no treatment in women with a prior fragility fracture. It also continues to dominate IV ibandronate but is dominated by zoledronate in women with and without prior fragility fractures with these costing assumptions.

Table 19

[redacted]



[redacted]

Table 20

[redacted]

[redacted]

6.2 Threshold analysis on the relative cost of denosumab versus zoledronate

[redacted]

[redacted]

[redacted]

Under the manufacturer's base case assumptions, denosumab is assigned admin/monitoring costs that are ~£127 per year lower than zoledronate's admin/moninotoring costs.

[redacted].

The above calculations were undertaken for a 70 year old cohort without prior fragility fractures (the lower risk cohort). In higher risk groups, admin and monitoring cost savings would have to be greater for denosumab to remain cost effective over zoledronate.

It is therefore vital to accurately establish what the true cost of administering these two drugs will be in practice.

6. 3 Subgroup analysis using secondary care costing assumptions for denosumab

Table 21, Table 22, Table 23 and Table 24 have been provided to show how the ICERs for densoumab change by subgroup using full secondary care costing assumptions for administration of denosumab and all the secondary comparators.

Table 21

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7. DISCUSSION – SOME ISSUES

7.1 Breast cancer risk

Raloxifene reduces the incidence of breast cancer, and one issue was whether the "side-benefits" of raloxifene should be included in the economic analysis. Had that been done, raloxifene would probably have dominated all other drugs.

The ERG asked Amgen for their reasons for not factoring in the breast cancer benefits. The response was as follows.

.....

> "In order to be consistent with the approach used to model the cost-effectiveness of raloxifene in NICE Technology Appraisal 161 (TA161) we have not included any reduction in breast cancer with raloxifene. Specifically, paragraph 4.2.11 of TA161 states that:
>
> *"For raloxifene, 4-year follow-up data from the MORE study were used, and it was assumed that women with low BMD have a lower breast cancer risk than women with normal BMD. The cost effectiveness was modelled excluding the breast cancer benefit, the risk of VTE and the effect on cardiovascular events.*
>
> Further paragraph 4.3.31 of TA161 states:
>
> *The Committee noted that a higher proportion of the overall benefit associated with raloxifene was attributable to its effect on the prevention of breast cancer than to its effect on the prevention of osteoporotic fragility fractures. The Committee agreed that, in principle, the side effects of using a drug should be considered; however, there were a number of reasons why the Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost-effective option for treatment for the secondary prevention of osteoporotic fragility fractures, as follows:*
>
> *• From the evidence presented, raloxifene was not as effective as the bisphosphonates for treating osteoporosis.*
>
> *• Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities.*

• Full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would require consideration of how it compares with other drugs that could be used for breast cancer prevention."

.....

Hence the Amgen case for not including the breast cancer benefits of raloxifene is based mainly on the precedent set by NICE.

A key point is that raloxifene was deemed to be not as effective in osteoporosis as other drugs. Hence if therapeutic decisions have to be taken about how best to treat women with osteoporosis and at high risk of breast cancer, the question which might be raised is whether to treat with a combination of a breast cancer risk reducing drug (e.g. tamoxifen) and a more effective osteoporosis drug than raloxifene. It might be that such women could get raloxifene to reduce breast cancer risk and a bisphosphonate for osteoporosis. The remit of this evidence review did not extend to consideration of such questions. It might be noted that tamoxifen, used for breast cancer prevention, has been found in a meta-analysis to reduces fractures to much the same extent as raloxifene[45] and is now in generic form.

Raloxifene has also recently been reported to improve memory in late post-menopausal women. [46]

A recent case/control study reported that bisphosphonates also reduced breast cancer incidence – odds ratio 0.67 (95% CI 0.51-0.89).[47]The authors adjusted for a number of possible confounding variables, but obviously could not adjust for unknown confounders. It may be that women most at risk of osteoporosis are at lower risk of breast cancer, in which case the reduction is not due to BPs. One possible explanation might be total exposure oestrogen throughout life. One unexplained finding in the study was that BPs were associated with a reduced breast cancer risk only in lean women. In obese women they were associated with increased breast cancer incidence.

7.2 Prevalence of osteoporosis

There has been speculation that reducing use of hormone replacement therapy might increase the prevalence of osteoporosis, and hence the market for bone loss drugs. Data from both the USA[48] and the UK[4,49,50] show that the prevalence of HRT use increased rapidly in the 1990s, from about 15% of women aged 45-69 in 1992 to 25% in the late 1990s[50] and then fell to 12.5% by 2006. Watson and colleagues used GPRD data to show that HRT use rose from 1991 to 1996, was stable 1997 to 2001, and has fallen by 50% from 2002.[4] Brewster and colleagues in Scotland noted that HRT use peaked in the late 1990s and then fell by 50% by 2005.[49]

The fall in the use of HRT followed the publication of the findings of the Women's Health Initiative trial, which showed an increased risk of breast cancer in women taking combined oestrogen and progestin.[50]

HRT is known to increase BMD and reduce hip fractures. Meyer and colleagues in Oslo noted that a rise in HRT use between 1979 and 1999 was followed by a 33% fall in Colles fractures and a 39% fall in hip fractures. They estimated that half of the fall might be due to HRT.[51]

Fisher and colleagues in Australia wondered if the fall in HRT use (by 55% in their region) would lead to a rise in hip fracture, but found a fall, which they attributed to the steep rise in BP use, since there was no fall in men. [52]

Watson and colleagues, using GPDR data, reported a rise in BP use from 0,2% of women over 40 in 1992, to 4% in 2005. There was an increase after the arrival of weekly alendronate, with 2.5% of women on weekly alendronate and 1% on weekly risedronate. The highest use was in the over 70s with 10% on BPs.[4]

7.3 Duration of treatment

There seems to be a common assumption in the literature that bone loss treatment is given for five years, and then stopped. The rationale for stopping it is not clear to the ERG. Black and colleagues [53] reported that women who continued alendronate after 5 years had a lower risk of vertebral fracture than those who stopped, but no difference in nonvertebral ones. BMD fell after cessation. They concluded that most women could stop after 5 years but those at highest risk might continue.

Naylor and colleagues reported that the benefit of raloxifene on BMD was lost six months after it was stopped.[54]

Geusens reviewed the literature on use beyond 5 years, and found only five studies, four with alendronate and one with risedronate. Longer treatment was associated with maintenance of BMD and bone turnover marker effects, but there was no convincing data on longer term fracture effects.[55]

The issue of whether a trial of 5 versus 10 years treatment with bisphosphonate would be worthwhile, has been explored by Stevenson and colleagues, and they concluded that one would be cost-effective for informing decision-making in the UK.[56]

7.4 Physical activity

Just for completeness, we note that physical activity helps reduce the decline in bone mass with age. A recent study from Tromso noted that physically active women had lost 36% of wrist BMD by the age of 80, whereas inactive women lost 56%. By the age of 80, the difference was estimated to be associated with an 85% increased fracture risk in the inactive women.[57]

7.5 High dose vitamin D

Also for completeness, we note the results of a trial of high dose vitamin D (100,000 IU oral vitamin D every four months for 5 years) by Trivedi and colleague swhich showed a reduction in all fractures of 22% and in major fractures (hip, forearm, vertebral) of 33%. [58] BMD was not obtained so comparative efficacy cannot be compared with most of the trials in this evidence review. However it could be an inexpensive intervention worthy of further study in post-menopausal women with confirmed osteoporosis.

7.6 Research needs

The main research needs are:

- monitoring long term safety
- duration of treatment – should it stop after 5 years, or should it continue in some subgroups?
- trials of denosumab compared to active comparators (especially zoledronate) with fractures as end points

7.8 Conclusion

The effectiveness of denosumab is not in doubt, and it appears safe. The key issue in cost-effectiveness analysis is its cost relative to zoledronate. For women with no prior fragility fractures, its potential cost-effectiveness relative to no treatment in some groups is also highly relevant, since current NICE guidance recommends no treatment for many women in this group if they cannot tolerate alendronate.

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APPENDIX

Appendix 1 Characteristics of trials used in indirect comparisons and DIVA study

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
FREEDOM Trial- Cummings NEJM 2009[11]	Multicentre (e.g. USA, Canada, Argentina, Brazil, Mexico, UK, etc)	Denosumab (60 mg every 3 months, SC)	3902	83.9%	72.3 (SD 5.2)	26.0 (4.1)	36 months	No prevalent vertebral fracture =73.4% Prevalent vertebral fracture =23.8%	New radiographic vertebral fractures	Time to the first non-vertebral fracture and the time to the first hip fracture.
		Placebo	3906	82.1%	72.3 (5.2)	26.0 (4.2)		No prevalent vertebral fracture =73.1% Prevalent vertebral fracture =23.4%		
HORIZON trial - Black 2007[12]	International, multicentre	Zoledronic acid -5 mg 15 minute infusion IV at baseline, 12 months	3875	83.8%	73.1 (5.34)	25.1 (4.3)	36 months	No prevalent vertebral fracture =37.6% 1 prevalent vertebral fracture =28.2% ≥ 2 prevalent vertebral fractures =24.1%	New vertebral fractures (in stratum 1 -i.e. patients not taking concomitant	Any non-vertbral fracture, any clinical fracture and clnical

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
		and 24 months							osteoporosis medications) and hip fracture (in both strata)	vertebral fracture
		Placebo	3861	84.7%	73.0 (5.4)	25.4 (4.3)		No prevalent vertebral fracture =35.8% 1 prevalent vertebral fracture =27.9% ≥ 2 prevalent vertebral fractures =36.3%		
TROPOS - Reginster 2008 [59]	75 centres in Australia and 11 European countries.	Strontium ranelate 2gm/day	2479	55.8%	76.7 (5.0)		60 months	1 prevalent vertebral fracture=32.6% 1 prevalent nonvertebral fracture = 39.3%	Incidence of osteoporosis related non-vertebral fractures	Hip fractures were analyzed post hoc in a subgroup of patients at high risk of hip fractures.
		Placebo	2456	54.2%	76.8 (5.0)			1 prevalent nonvertebral fracture = 37.8% 1 prevalent vertebral fracture=34.5%		

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
SOTI Study - Meunier 2004[60]	72 centers in 11 European countries and Australia	Strontium ranelate 2gm/day	719	87.3%	69.4 (7.2)	26.1 (4.1)	36 months	100% had a previous fracture Mean number of previous vertebral fractures =2.16 Percentage of previous non-vertebral fracture =33.7%	Vertebral fractures	
		Placebo	723	87.4%	69.2 (7.3)	26.2 (4.1)		100% had a previous fracture Mean number of previous vertebral fractures =2.20 Percentage of previous non-vertebral fracture =32.0%		
MORE Study - Ettinger 1999[61]	Multicenter, international trial	Raloxifene hydrochloride 60 mg/day (Study 1)	3002	77.5% (Groups 1 & 2 combined)	65 (7)	25.0 (3.9)	36 months	Existing vertebral fractures:0 = 88.7%; 1 = 9.6%; ≥2 = 1.7%	Incident vertebral fractures and bone mineral density	Any nonvertebral fracture
		Placebo (Study 1)	1522	74.7% (Group	65 (7)	25.0 (3.9)		Existing vertebral fractures: 0 = 89.9%; 1 = 8.3%; ≥2 =		

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
				s 1 & 2 combined)				1.7%		
		Raloxifene hydrochloride 120 mg/day (Study 2)	1534		68 (7)	25.8 (4.2)		Existing vertebral fractures: 0 = 10.0%; 1 = 40.4%; ≥2 = 49.6%		
		Placebo (Study 2)	770		68 (6)	25.8 (3.9)		Existing vertebral fractures: 0 = 11.6%; 1 = 40.5%; ≥2 = 47.9%		
Lufkin 1998[62]	All participants were studied at the Mayo Clinic, Rochester, or the Mayo Clinic,	Raloxifene 60 mg/day	48		69.9 (0.5)	24.8 (0.61)	12 months	Median Number of prevalent vertebral fractures: (>30% cutoff definition) = 1 (>15% cutoff definition) = 5.5	BMD and fractures? (not explicitly stated)	
		Raloxifene 120 mg/day	47		67.2 (0.9)	26.2 (0.70)		Median Number of prevalent vertebral fractures: (>30% cutoff definition) = 1		

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
	Scottsdale.							(>15% cutoff definition) = 5.0		
		Placebo	48		68.2 (0.7)	25.3 (0.55)		Median Number of prevalent vertebral fractures: (>30% cutoff definition) = 1 (>15% cutoff definition) = 4.5		
Morii 2003[63]	Japan; 26 study sites	Raloxifene 60 mg/day	92	85.9%	65.2 (6.2)	21.5 (2.4)	12 months	Prevalent vertebral fracture = 24%	Lumbar spine BMD and overall safety	Biochemical markers of bone turnover
		Raloxifene 120 mg/day	95	85.3%	64.7 (6.2)	21.9 (3.0)		Prevalent vertebral fracture = 27%		
		Placebo	97	89.7%	64.3 (6.5)	22.0 (3.0)		Prevalent vertebral fracture = 27%		
Silverman 2008[64]	206 sites in Asia-Pacific countries, Canada, Europe, Latin	Raloxifene 60 mg/day	1849	67.7%	66.4 (6.7)	26.4 (3.8)	36 months	Prevalent vertebral fracture = 56.3%	Incidence of new vertebral fractures	Non-vertebral fractures, BMD and bone
		Placebo	1885	66.6%	66.5 (6.8)	26.3 (3.8)		Prevalent vertebral fracture = 56.4%		

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
	America, South Africa, and the United States.									turnover markers
Liu 2004[33]	3 investigative sites in China	Raloxifene 60 mg/day	102	95.1%	65.5 (6.5)	23.0 (2.9)	12 months	Prevalent vertebral fractures: in thoracic region = 10.8% in lumbar region = 8.8%	Percentage change in lumbar spine BMD	
		Placebo	102	90.2%	65.1 (5.4)	22.9 (3.0)		Prevalent vertebral fractures: in thoracic region = 9.8% in lumbar region = 5.9%		
BONE Study - Chestnut 2004[65]	73 centers in Europe and North America.	Ibandronate, oral, 2.5 mg daily	977	66.3%	69 (6)		36 months	Percentage with one fracture =94% Percentage with two fractures =44%	New morphometric vertebral fractures	New or worsening vertebral fractures, clinical vertebral fractures, nonvertebral
		Ibandronate, oral, intermittently	977	67.8%	69 (6)			Percentage with one fracture =94% Percentage with two fractures =42%		

Reference	Population	Interventions	No. in ITT population	% completing	Age - mean (SD)	Mean BMI (SD)	Duration	Previous fractures	Primary endpoints	Secondary endpoints
		Placebo	975	64.4%	69 (6)			Percentage with one fracture =93% Percentage with two fractures =43%		fractures; BMD; bone turnover; changes in height.
FPT Study-Neer 2001[66]	99 centers in 17 countries.	Teriperatide (paraththyroid hormone (1-34) 20 µg	541	82.1%	~70	~26.5	median duration of observation 21 months	Number of vertebral fractures = ~2.4	Fractures (but not explicitly stated)	
		Teriperatide (paraththyroid hormone (1-34) 40 µg	552	78.6%	~70	~26.6		Number of vertebral fractures = ~2.3		
		Placebo	544	82.4%	~69	~26		Number of vertebral fractures = ~2.4		

DIVA Study-Eisman 2008[13]	A total of 58 centers in North America, Mexico, Europe, Australia and South Africa.	Ibandronate, IV (2 mg every 2 mo)	454	79.5 %	66.5 (6.2)	25.7 (4.0)	24 months	Previous fracture since age 45 yrs = 41.8%	Mean change (%) from baseline in lumbar spine (L2–L4) BMD after 1 year.	Mean change (%) from baseline in lumbar spine (L2–L4) BMD and proximal femur BMD after 2 years.
		Ibandronate, IV (3 mg every 3 mo)	471	79.0 %	65.6 (6.2)	25.6 (4.3)		Previous fracture since age 45 yrs = 42.9%		
		Ibandronate, oral, 2.5 mg daily	470	81.7 %	65.6 (6.1)	25.3 (4.3)		Previous fracture since age 45 yrs = 44.4%		